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Chemistry-Related Innovations in Space, Benefits of Flow Chemistry

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6.1 Introduction

Space chemistry is an emerging field, i.e., performing chemistry in space as distinguished from astrochemistry or planetary chemistry. First, our chapter discusses the unique properties (microgravity, low temperature, cosmic ray) of space pointing out the extraordinary chemistry opportunities. Furthermore, the radical expansion of space industry in the last decades has been generating the scientific, technological, and also commercial infrastructure for realizing chemical processes in space.

The "drug-on-demand" capacity will supply astronauts on long-duration spaceflights with the necessary pharmaceuticals, and the deep understanding of the cellular and disease mechanisms also play an important role in developing countermeasures to mediate the response to microgravity and/or space radiation. The exploitation of the advantages of microgravity in protein crystallization and formulation is a rapidly developing area in the space pharma sector; various examples demonstrate that drug uniformity stability has been increased.

Electrochemical CO_2 conversion in space allows to recover oxygen from exhaled carbon dioxide, while generating useful carbon-based products. These processes are extremely important for present and future missions in space.

6.2 Challenges of Chemistry Realized in Space

Space chemistry, as a major component for the presently available space technologies, and even more importantly, as a growing field with many surprises and

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promises for the future, has already provided several results which may affect not only the future development of space chemistry itself, but also our understanding of chemistry in general. In our interpretation of the details and the underlying scientific relations of space chemistry, molecular modeling approaches, with a strong quantum chemistry foundation, will have a major role.

Some of the not fully explained and unusual aspects of chemical and biochemical processes observed in satellites and during space experiments on the International Space Station (ISS) are bringing up some fundamental questions concerning the possibilities that some of the expected features of such processes, based on the accumulated experiences and interpretations on the surface or near to the surface of Earth, are affected by some of our biases.

6.2.1 Unique Features of Space: Lack of Directionality (Cosmic Rays, Microgravity)

The most natural is to focus on the differences in the levels of intensity of cosmic rays as well as on the manifestations of gravity in the two types of environments. Many aspects of radiation chemistry have been well studied for a wide range of radiation types, including cosmic rays, on the other hand, much less emphasis has been placed on a very “natural” condition, usually taken for granted: the role of the gravity of the Earth.

One special aspect of gravity may play a role: the presence of a dominant directionality of gravitational forces near the surface of the Earth. This directionality is far less important in space, at a larger distance from the center of the Earth, than it is within the “usual” environment near the Earth’s surface, where most of our experiences and scientific development have taken place during our past history. On the other hand, even the radiation effects from cosmic rays are affected by differences not only in intensity, but also by differences in directionality, if one moves away from the surface of the Earth to space. By being at a significant distance away from the Earth, the dominant “from up to down” directionality of cosmic rays on the surface of the Earth is replaced by a more multidirectional radiation; hence, again, in space there is a much lesser dominance of directionality for cosmic rays, just as a much lesser dominance of directionality for the role of gravity. One aspect of the lesser dominance of directionality is likely to be manifested in a fuller realization of randomness, if the direction of “downward” is having a far lesser significance. Entropy, and the manifestation and role of randomness are not independent of the presence or lack of a dominant direction (and of the actual level of its dominance). In the space, this is likely to have some effect even on chemical reactions, and ultimately, the chemistry contribution to space technologies. There is strong evidence from studies on reaction features affected by hydrodynamic instabilities arising in horizontally propagating vertical chemical fronts that dominant directionality often gives rise to some unexpected features (Pópity-Tóth et al. 2013), also providing additional information in more recent studies on reactive fronts in modulated gravity environment (Horváth et al. 2014, pp. 26279–26287) and specifically in microgravity (Bába et al. 2018; Bába et al. 2019, pp. 406–412). Directionality of injections relative to chemical fronts (Tóth et al. 2020, pp. 10278–10285) has a specific role that is influenced by higher or lesser dominance of directionality effects.

6.2.2 Theoretical Aspects: Quantum Chemistry Approach

How molecules can modify their shapes even from relatively weak forces (Mezey 1993), how their parts interact (Mezey 1999, pp. 169–178), and even the details of chemical reactions can be modeled rather accurately by quantum chemistry methodologies. Concerning space chemistry, various constraints, such as local forces acting on individual atoms in a molecule, additionally to the usual forces of chemical bonds keeping the parts of the molecule together and being responsible for the various vibrational motions can be introduced, to see how a change in the role of the directionality of gravity may influence molecular behavior.

Molecular shapes, their variations during actual molecular vibrations, their conformational changes which may actually play a major role in space chemistry, where even weak effects are assumed to be able to influence molecular behavior in dominant way, and the actual distortions of molecular atomic arrangements during chemical reactions have been studied in great detail by quantum chemistry calculations, providing precise descriptions how individual atomic nuclei move relative to the other atomic nuclei in such processes (Mezey 1993; Mezey 1999, pp. 169–178). What is relevant to our present problem, it is also possible to introduce some artificial forces on individual atomic nuclei, imitating some enhancement of directional forces, or introducing atomic mass dependent counter-forces, in order to gain understanding of the actual effects of the presence of “privileged” directions, such as “downward” direction. The model of assumedly “unbiased” randomness of orientations of molecules in a solution can be tested and possibly refined by such computations.

For example, by introducing artificial “counter-forces” into such quantum chemistry models, and modeling their effects on the speed and outcome of chemical reactions, or, on the speed of development in crystallization and the lesser frequency of local irregularities in crystal grows, can provide new hints how to interpret and exploit better some of the remarkable and unexpected phenomena in space chemistry. Besides learning from actual quantum chemistry modeling approaches, such models may also motivate new experiments. For example, when the effects of one type of change are studied, it is often useful to study the exactly opposite effect. In our case, by imitating the effects of much higher levels of gravity on chemical reactions and crystal growth. Whereas placing chemical experiments within environments of much higher gravity, such as it is present near the planet Jupiter is technically not yet feasible, nevertheless, by using experiments in centrifuges: by placing the chemically reacting molecules as well as the monitoring equipment within a centrifuge, one may imitate high-gravity environments, and when compared to conditions on Earth, a far more dominant effect of forces with dominant directionality (within the rotating system) can be achieved that may help to explain the opposite phenomenon: the lesser dominance of directionality in space chemistry.

In space chemistry, the role of symmetry may also deserve special attention: if a dominant directionality, such as the direction of the force of gravity, is of lesser importance, this fact alone may indicate that possibly, a better approximation to perfect symmetry is manifested there. As follows from quantum chemistry studies of approximate symmetries and symmetry deficiency measures for molecules (Lijie et al. 2006, pp. 145–153; Mezey et al. 1998, pp. 99–105), the distortions of molecular parts have strong relations with the distortions of the entire molecules. For example, locally no perfect mirror plane can exist for any CH_2 group in any molecule, if the complete molecule does not have a mirror plane. Especially, measures for the degree of chirality may also be affected by the reduced role of the directional forces of gravity in space chemistry that may also affect some selectivity aspects of chemical reactions, for example, in polypeptide or protein synthesis reactions. Symmetry and chirality are suggested for special investigations within the space chemistry context.

An alternative approach may involve reaction studies along surfaces where directionalities can be monitored macroscopically, or those catalytic reactions involving zeolites. If such studies are carried out in space, or in a centrifuge, the directionality effects can be studied from a new perspective. For example, if the zeolite framework is given, and the actual reactions occur within the cavities of zeolites, then the directionality constraints within zeolites cavities, with possible enhancement or hindrance of the directionality bias represented by gravity or by centrifugal forces can provide a combination that may reveal some new aspects of space chemistry. Earlier quantum chemistry studies on zeolites have provided some insight for the non-random distribution of the Si and Al atoms within their frameworks (Hass et al. 1981, pp. 389–399; Mezey 1984 pp. 147–156; Derouane et al. pp.145–156), providing a quantum chemistry explanation of the so-called Loewenstein rule on zeolites: in these alumino-silicates the statistically expected Al–O–Al linkages do not occur, as such linkages would be not only energetically unfavorable, but would also generate a major strain within the zeolite framework, adding to the forces already present, that in the space-chemistry context would involve the modified forces of gravity.

The randomly taken few examples here in this section serve just to illustrate the deep world of the theoretical questions which are emerging when chemistry is performed in space. It is expected that theoretical chemists are going to focus more on responding to the emerging number of the challenging and sometimes astonishing observations which are gathered during systematic on orbit chemical experimentations. See, for example, the comment on the difference in bubble formation on orbit and in the Earth, furthermore its practical consequences, see below.

6.3 Space Chemistry – Concept, Historical Summary, and Current Efforts

Space chemistry, for decades, has been equivalent to astrochemistry or planetary chemistry (i.e. the study of the chemical behavior of atoms and molecules in space or on planets) (Yamamoto 2017; Rehder 2011). Today, the term space chemistry is applied for *performing* chemistry in space. The radical expansion of space industry in the last decades has been generating the scientific, technological, and also commercial infrastructure for realizing chemical processes, like syntheses and analyses in space. It has become necessary to develop novel chemical compounds, formulation methodologies and/or reaction routes, for supporting space traveling, drug discovery and manufacturing, developing effective ISRU processes, initiating asteroid and planet mining (Hessel et al. 2021, pp. 3368–3388; Wouters et al. 2021, pp. 118238–118252), all in an off-Earth environment.

6.3.1 Foundation of the Space Chemistry Consortium

A significant step toward bringing chemistry to space was realized in 2014 by the International Flow Chemistry Society (www.flowchemistrysociety.com) that initiated the worldwide academic–industrial Space Chemistry Consortium (https://innostudio.org/space-chemistry-consortium) at an informal meeting associated with the IMRET13 Conference in Budapest (IMRET13 2014). The Consortium targeted to bring together people from the chemical community interested in doing chemistry in space. The founders' common denominator was their experience and proficiency in flow chemistry and microfluidics; furthermore, their shared view was that these two fields can solve elementary process issues (like imperfect mixing) impeding the chemical experimentation in space for decades. The initial targets of the Consortium were formulated as follows (FROST5 2015):

1. Create a standardized and flexible space laboratory with a capability for a wide range of chemistry discoveries coupled with plug and play "pharmacy on demand" chemistry system (transition from individual to cascade reactors) where pharmaceuticals are synthesized, analyzed, purified, and formulated when needed.
2. Create new chemistry in space: Utilize the extreme conditions of space (tunneling effect) on different chemical processes to discover new routes to novel molecules or more efficient chemical applications.
3. Recycle biological waste (especially carbon monoxide to oxygen). Convert human biological waste materials to reusable chemicals in order to sustain human life.

These objectives of the Consortium harmonize well with the global space research goals of the International Space Exploration Coordination Group (ISECG) (www.globalspaceexploration.org). The Consortium since then has grown to a substantial organization of more than 40 internationally renowned members from academia and industry exerting influence to the newly born space chemistry community. One of the most important and early results of the Space Chemistry Consortium was to create a scientific platform in order to share the latest advancements and results of performing chemistry in space. Together with the Flow Chemistry Society, the Consortium approached the American Chemical Society (as the world's largest chemical association) and initiated the Space Chemistry Symposium series (https://innostudio.org/space-chemistry-symposium) that has regularly been held since 2015 as part of the ACS National Meeting and Exposition. The event is dedicated to key topics and research areas such as pharmaceutical production in space, flow chemical reactors and syntheses for space applications, chemical instruments and analytics for microgravity environment, CO_2 capturing and transformation for applications on Mars, and in-space manufacturing of diverse materials and chemicals. In April 2021, the 6th Symposium was held, keeping the ACS Space Chemistry Symposia the world No.1 scientific event for the space chemistry community today.

6.3.2 Recent Activities and Successes in Space Chemistry

Scientific literature within the topic of performing chemistry in space so far has been scarce. The first papers about the overall concept and promises of flow chemistry for microgravity applications were published by the ThalesNano Group together with the University of Szeged (Jones et al. 2017, pp. 1–3; Sipos et al. 2017, pp. 151–156) where the authors proposed a scheme to prioritize chemical experimentations in space (see Figure 6.1).

The history of chemical experimentation in space goes back to a half century. One of the first, chemistry-related "experiments," although unplanned, had taken place in the lunar module of Apollo 13, which saved the lives of the crew. Following explosion of one of the oxygen tanks in the spacecraft, a makeshift adaptor for the lithium hydroxide canisters to remove toxic CO_2 build-up was made out of space parts, and

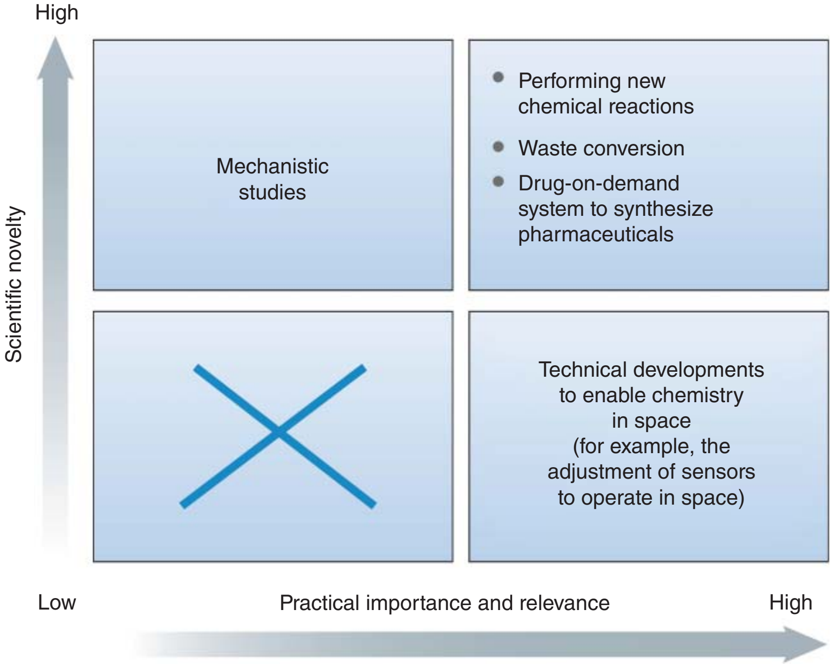


Figure 6.1 Selection criteria for chemical experiments to be performed in space. Source: Republished with permission of Jones et al. 2017, Springer Nature.

residual power from batteries was used to restart the command module and take the crew back to Earth (Li 2018). In the following three decades, sporadic experiments related to chemical research were carried out on Salyut 6, Mir, and the Space Shuttle. One of the earliest chemical reactions investigated on the ISS was about the combustion of fuels (Williams 2017). Mattioda and coworkers first reported photostability results of organic compounds in orbit, including a polycyclic aromatic hydrocarbon, amino acid, metalloporphyrin, and quinone (Mattioda et al. 2012, pp. 841–853).

In the last years, chemistry-related scientific research in space and for space purposes has gained wide interest – that is not surprising, considering the improved access opportunities to space platforms (Joseph and Wood 2021, pp. 123–138). The Israeli–Swiss company SpacePharma (www.space4p.com) developed a miniaturized and remotely controlled laboratory system which can be utilized to conduct diverse research experiments under microgravity either on satellites, spacecraft, or on the ISS. Chemistry-related experiments in SpacePharma's equipment have included enzymatic oxidation, drop coalescence study, and also crystallization (Samburski 2020). One recent experiment on the ISS by researchers from The Pennsylvania State University included mixing an aqueous solution with tricalcium silicate for the first time, in order to study how the chemistry of concrete is changed by microgravity (Neves et al. 2019, pp. 1–12). Understanding how concrete works in space has direct bearing on future plans regarding building on the Moon and Mars.

The Beeler Research Group (www.beelerlab.com) at Boston University, partnering with Space Tango (spacetango.com), investigated three fully automated chemical reactions on the ISS and made the first effort to synthesize organic compounds onboard (Beeler 2020). The University of Adelaide has recently teamed up with Space Tango and Alpha Space (www.alphaspace.com) to conduct a pharmaceutical stability study on ISS (Rosales 2020). The expected results will allow to generate highly innovative data sets that will help direct the future in-orbit and on-demand production of medicines. The first anti-COVID-19 experiments in space were recently carried out in the European module on ISS (ESA 2020). The promising study has recently been led by InnoStudio (www.innostudio.org) and CycloLab (www.cyclolab.hu), in collaboration with Japan Manned Space Systems Corporation (www.jamss.co.jp) and Space Applications Services (www.spaceapplications.com). The researchers, among others, investigated how remdesivir, the active ingredient of the COVID medicine Veklury (www.gilead.com), interacts with its solubilizing cyclodextrin derivative in order to improve the drug's efficiency.

Chemical experimentation is already present on Mars: the MOXIE experiment (see Section 6.6), developed by NASA, is using a device that extracts small amounts of oxygen from the Martian atmosphere via electrolysis (https://mars.nasa.gov/mars2020/spacecraft/instruments/moxie/).

Space agencies today are expecting more science teams to collaborate with industry in order to accelerate their research and development efforts by using commercial space-based platforms on a more intensive level. This trend in parallel defines the urgent need for designing and setting up platforms ensuring chemical experimentation, syntheses and research in space.

6.4 Space Chemistry Results: Life Sciences, Pharma Industry, Agro Industry, Cosmetics, and Others

Space chemistry is presently the single available approach to create a “drug-on-demand” production system in space in which a variety of pharmaceuticals can be synthesized, analyzed, purified, and formulated fresh on orbit when needed. The “drug-on-demand” capacity will supply astronauts on long-duration spaceflights with the necessary pharmaceuticals. It is also expected that flow chemistry in space will allow development of more efficient drugs, syntheses and formulation processes, and new molecules by known chemical reaction or by novel routes (Mezohegyi et al. 2021).

In the area of life sciences, the primary goal is the deep understanding of the cellular and disease mechanisms, biological pathways, and potential protein targets that play a role in mediating the response to microgravity and/or space radiation (Braddock 2020; Ruyters et al. 2017; Ryder and Braddock 2020).

It seems the unique conditions of human spaceflight require substantial biological adaptation (Schmidt et al. 2019). After a year-long spaceflight an extensive study conducted by NASA led to the conclusion that microgravity produces numerous changes in the musculoskeletal, visual, and immune systems, including decreased body mass, bone density, elongation of telomeres, genome instability, transcriptional and metabolic changes, altered drug-drug interactions, and drug resistance (Garrett-Bakelman et al. 2019).

One particular area is to investigate the immune response and drug resistance during space flights. Many reports underline that the immune system in astronauts may be reduced, including suppressive effects on mediators, change in leukocyte distribution, and reduction in T cell function. Determination of the effective dose of antibiotics in microgravity is particularly important while exposing to pathogens. Tissue engineering in space (e.g. three-dimensional aggregates from different cell types) is another potential area of the applied life science developing novel regenerative medicine tools.

6.4.1 Investigating and Exploiting Microgravity Effects

The pharma industry benefited much from the innovative space technologies in many ways; for example, identification of protein targets involved in complications occurring during spaceflights or in enhancing human radio-resistance is particularly important. Rapid alteration in gene expression in osteoblasts and the atrophy tissue metabolism in space help the understanding of the aging process on earth and could lead to the development of novel drugs and therapies (Braddock 2017). Indeed, cardiovascular, musculoskeletal, nervous, gastrointestinal, and immune responses to microgravity are similar to changes associated with aging, but seem to occur about 10 times faster in space than on Earth (Demontis et al. 2017, pp. 547).

The exploitation of the advantages of microgravity in protein crystallization is a very rapidly developing area in the space pharma sector (Reichert et al.

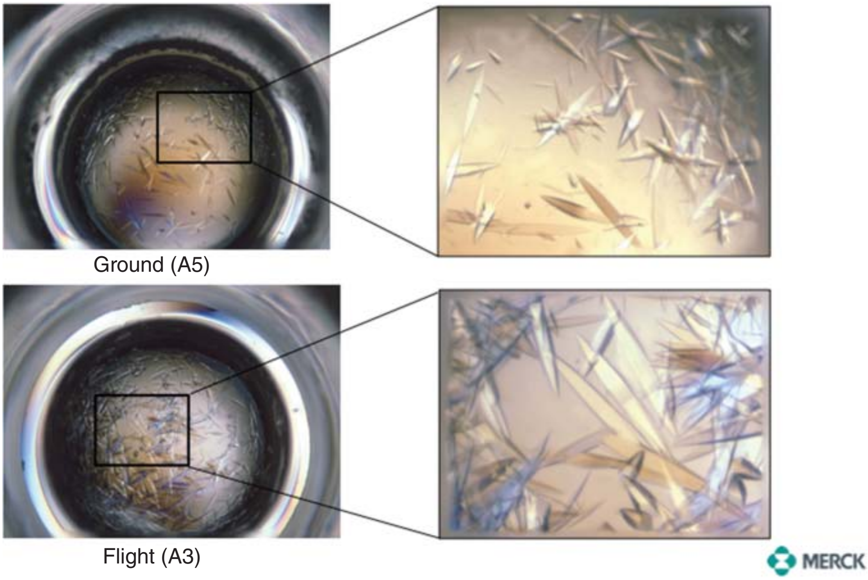


Figure 6.2 Differences in crystal size and morphology of monoclonal antibodies in space and on earth (Merck experience: https://www.nasa.gov/mission_pages/station/research/benefits/mab/). Source: NASA.

2019, pp. 1–8). Structure-based drug discovery relies on the 3D structure of the protein–ligand interaction (Figure 6.2).

Most protein structures are determined by X-ray crystallography, which requires diffraction-quality protein crystals. Convective currents and sedimentation occur under gravity and disturb crystal growth; thus, producing diffraction-quality protein crystals is a particular challenge (Moreno 2017, pp. 51–76). Microgravity has produced crystals that grow larger with more regular morphology and diffract to higher resolution than crystals of the same proteins grown on Earth (McPherson and DeLucas 2015). Furthermore, producing ultra-pure, crystalline biological medicines (e.g. therapeutic antibodies) in space has much potential. The drug substance is often stored as frozen diluted solutions or frozen lyophilized powders. For areas of the world, where refrigeration is limited, stable, high-purity crystalline drug substances are needed (Daugherty and Mrsny 2010, pp. 103–129), and only crystallization of proteins in space could provide such quality (Reichert et al. 2019, pp. 1–8).

In the area of drug formulation producing new polymorphs and co-crystals could enhance druggability and activity of existing or new active chemical ingredients (Yamaguchi et al. 2021). See details in Section 6.5.

Lyophilization is commonly used in drug formulation to increase the chemical and physical stability of pharmaceutical products. Pharma companies are interested in understanding what effects gravity has on the properties and physical state of lyophilized materials (http://www.iss-casis.org/iss360/taking-chemistry-out-of-this-world/).

6.4.2 Drug Stability in Space

Drug stability during space flights is the other critical issue. Astronauts going to long-term space travels or staying on the Moon and Mars are facing the problems of the fast decomposition of active pharmaceutical ingredients (APIs) in space (Mehta and Bhayani 2017, pp. 111–119). Medicines should remain active at least up to their designated Earth shelf-life and should be protected from the degradation caused by the radiation in space. An alternative solution is the on-demand continuous manufacturing of APIs. On-site-on-demand production of chemicals are immediately used after generation (Dallinger et al. 2020, pp. 1330–1341). A robotically controlled experimental flow chemistry platform, combining artificial intelligence, with planning and self-optimization, quality control and formulation (Coley et al. 2019) could be useful in space.

Solar concentrators which led to photomicroreactors seem to be an appropriate tool for pharmaceutical, chemical, and fuel production in space (Noël 2021). Space chemistry furthermore allows the study of chemical reactions that exploit the harsh conditions (such as vacuum, high-intensity UV radiation, extreme temperatures, and microgravity) that are prevalent in outer space. Flow chemical technology seems to be suitable to support *in situ* resources utilization (ISRU) (Schlüter and Cowley 2020; Starr and Muscatello 2020, Advincula 2019) and also in-space propellant production (Kornuta et al. 2019).

When talking to medicinal chemists at conferences, and reading the overly dispersed literature on on-orbit applications of space chemistry, it is easy to draw the conclusion that after the first breakthrough results the interest for chemistry-related space applications will increase enormously.

6.5 Space Chemistry Results: Formulation

Formulation has vital role in several industries, like pharmaceutical (Devalapally et al. 2007, pp. 2547–2565), agricultural (DeRosa et al. 2010, p. 91), food (Chaudhry et al. 2017), and cosmetics (Santos et al. 2019, pp. 313–330), to name a few. Generally, an active ingredient cannot be utilized by itself without formulation because of its chemical stability, low solubility under physiological conditions, biocompatibility, volatility, or other factors. In addition, the release of an active ingredient often needs to be controlled in time and/or needs to be target specific.

Crystallization has been researched for a long time and it was among the first topics in the fields of space chemistry and space chemical technology (see also Section 6.4). The first space crystallization results were obtained by the Apollo experiments more than 50 years ago, where the role of microgravity in this process has been revealed (Walter 2012). At the beginning of space crystallization experiments (Benz and Dold 2002, pp. 1638–1645) three challenges emerged:

(1) How to apply the same experimental conditions on Earth and in space?
(2) Are the optimal conditions for crystallization under microgravity the same as on Earth?

(3) Since in most cases microgravity experiments are singular, what kind of statistical approach at data processing can be applied?

6.5.1 Crystallization in Space

In the meantime, numerous microgravity platforms have been developed for space research, such as the American Skylab, the Spacelab missions, D1 and D2 missions (Germany), the Japanese sounding rocket programs (Benz and Dold 2002, pp. 1638–1645), and a Chinese platform (Chen et al. 2001, pp. 478–479). While the platforms and crystallization equipment underwent vital evolution over time, the research targets have also changed. Nowadays, the use of microgravity is not considered anymore as the Holy Grail for perfect crystal growth, but still it remained a significant opportunity in improving crystal quality (McPherson and DeLucas 2015).

Crystallization in space has soon triggered the development of special instrumentations. An experiment based on the TEXUS hardware was flown on STS-9 in 1983 and grew crystals of lysozyme and β-galactosidase (Littke and John 1986). The Vapor Diffusion Apparatus (VDA), invented by the University of Alabama (Birmingham, USA) first flew in 1985 (DeLucas et al. 1986). The design of this hardware was meant to mimic the hanging drop vapor diffusion experiments most utilized for crystallization on Earth (Karr et al. 2015). The device enabled to maintain 24 experiments with no temperature stabilization and/or control capability. The use of VDA resulted in crystals of significantly higher quality than of the terrestrial ones. The second generation of VDA equipment was able to keep constant temperature at 4 or 22 °C and maintain 3 × 20 vapor diffusion experiments (DeLucas et al. 1986, pp. 681–693).

The STS-42 (International Microgravity Laboratory), flown in 1992, was the first flight dedicated to the maintenance of a microgravity environment. On this flight, both VDA and the German Cryostat (liquid-liquid diffusion) hardware were flown. In the Cryostat, a Satellite Tobacco Mosaic Virus (STMV) crystal was produced that was 30 times larger than any of the STMV crystals ever been grown on Earth (Karr et al. 2015). Nowadays, microgravity crystallization entered into the commercial phase, where affordability is a key factor to encourage industry to explore crystallization in space. The Japan Manned Space Systems Corporation provides a high-quality protein crystal growth service, so-called Kirara. The 1U (https://www.nasa.gov/content/what-are-smallsats-and-cubesats) volumed incubator is able to maintain 96 individual experiments at fix 20 °C (Sato 2020). The "Kirara box" has a dedicated platform on the ISS, in which some of the present authors performed formulation related research successfully, including protein crystallization, co-crystal formation for small molecules, and also optimization of an anti-SARS-CoV-2 drug formulation with remdesivir and certain cyclodextrin derivatives.

Three particular application areas of space crystallization are worth mention: protein crystallization, co-crystal formation, and inorganic crystal formation.

In the past decades X-ray crystallography underwent a vital evolution. The time required for structural analysis decreased from days/weeks to hours which encouraged the researchers to prepare more and more complex structures (Pflugrath 1992, pp. 811–815). Preparation and structural investigation of protein crystals has vital contribution to medicinal chemistry, especially to the target identification (Braddock 2020). Meanwhile, the parallel/high throughput crystal growing methods have also undergone meaningful development with automatization targeting the preparation and analysis (Deller and Rupp 2014, pp. 133–155). Formation of co-crystals has vital importance in the pharmaceutical industry. These structures can be made up of small specimens (molecules, ions), macromolecules (proteins, polymers), and the combination of these compounds. In the field of drug discovery, co-crystals have an important role in target identification, where the protein is crystallized in the presence of nucleic acids, small molecules, or drug candidates (Zheng et al. 2014, pp. 125–137).

Semiconductor materials have wide interest in the industrial field. Enhancing the optical, electrical, and magnetic properties of them has been an evergreen topic up to now. In the early stage of space crystallography experiments, many experiments have been conducted for the improvement of crystalline semiconductors in space (Benz and Dold 2002, pp. 1638–1645). On-board microchip synthesis of nanocrystalline quantum dots have been proposed in order to apply as a spectral decoy to divert rocket attacks. (Nijhuis et al. 2021, pp. 471–485).

In 1993, the German Spacelab mission D-2 GaAs crystal growth experiments have been launched by the German Space Agency. Using floating-zone technique the obtained sample contained significantly lower amount of dislocation networks with relatively larger cell size than its Earth-growth counterpart (Herrmann and Müller 1995, pp. 350–360). In the same mission, Cröll et al. also reported about decreasing dislocations in the case of GaSb using floating-zone method (1998, p. 365). In 2001, a Chinese research group reported on GaAs crystals with considerably better electrical properties after crystallization in space compared to their terrestrial grown reference samples (Chen et al. 2001, pp. 478–479).

6.5.2 Nanoformulation in Space

Among the several formulation techniques, nanotechnology is one of the most promising methods to enhance druggability, increase chemical stability (Dantuma et al. 2015), and enable target specific formulae, especially in the field of cancer treatment. Since the SARS-CoV-2 outbreak, nanotechnology-based medicines have received considerable attention because mRNA-based vaccines use lipid nanoparticles as carrier for increasing stability and bioavailability (Laczkó et al. 2020, pp. 724–732). Nanoformulation can be done by flow chemical instruments which provide precise drug load and size regulation, continuous manufacturing, and easy handling. Organic flow nanoformulation technologies are on the market as well, for example the Canadian Precision Nanosystems NanoAssemblr® platform that is suitable for nano vaccine synthesis using lipid nanoparticles (Walsh et al. 2014, pp. 109–120). The present authors also have a patented technology which is called SpeedyNano® platform (Manek et al. 2019), in which the nanonized organic compound is embedded in a biocompatible polymer matrix. This method is based on the so-called flash nanoprecipitations, where the composite particle is formed *in situ* by the supersaturation of the active ingredient. The selection of appropriate chemical composition, type of polymer, and flow rate depends on plenty of factors. Artificial intelligence is essential to reduce the number of experiments during the optimization phase.

Colonies in space and on Mars would require vast quantities of food; therefore, growing plants in a greenhouse is the adequate solution. Tailored fertilizers and specific types of bacteria and fungi are beneficial for plant cultivation. However, contamination and mutation would lead to microorganism that are harmful to the plantation and require specific protective agents. On-demand synthesis and nanoformulation of agrochemicals would be essential (Manek et al. 2019).

In summary, we believe that the significance of formulations performed in space will continue to grow rapidly and within a few years crystallization, co-crystal formation, clathrate formation, nanoformulation, and others will be part of the routine toolkit of the formulation experts.

6.6 Electrochemical CO_2 Conversion in Space: a Key Step to *In Situ* Resource Utilization

To recover oxygen from exhaled carbon dioxide, while generating useful carbon-based products is of high importance both at the International Space Station (ISS) and possibly for future missions (Jones et al. 2017). NASA has the current CO_2 Reduction Assembly (CRA) fully operational on-board the ISS since 2011 (Nelson et al. 2020) as part of the Environmental Control and Life Support System (ECLSS). The CRA is based on the Sabatier reaction ($CO_2 + 4H_2 \rightarrow CH_4 + 2H_2O$), to convert CO_2 to methane (CH_4) and water. The water produced is fed to the water purification system and then to an electrolyzer system to produce H_2 and O_2. Hydrogen is recycled to the CRA, O_2 is released into the cabin, and CH_4 is vented externally. The CRA recovers less than 50% of O_2 from CO_2 due to H_2 loss in the vented CH_4 (Nelson et al. 2020). However, there is an urgent need for new technologies that can increase the oxygen recovery rate to at least 75% or more. A better recovery rate means less oxygen needs to be stored and would free up precious cargo space on prolonged (Mars) missions. Finally, as an additional strategic motivation, we mention that if mankind ever aims to colonize Mars, the key available feedstock for any chemical reactions will be CO_2, which represents 96% of the Martian atmosphere (Rapp 2008).

Electrochemical processes in space offer a way to form valuable chemicals with no by-product formation, and without using additional chemicals. Different oxidation and reduction powers can be achieved just by changing the cell voltage (Nelson et al. 2020). Beyond the well-established water splitting, CO_2 conversion, C—C coupling reactions, CO addition or even the synthesis of pharmaceutical compounds can be achieved. The abundance of solar radiation and our ability to convert significant fractions of it to electrical power enables the use of electrical power for electrochemical life support and also in-situ electrochemical material processing. Such processes use water and carbon dioxide as reactants and produces oxygen (on the anode) and small organic molecules, such as ethylene or methanol (on the cathode). The gases can be vented into space (or used for other chemical purposes) and the oxygen is used for breathing. In terms of thermodynamics of the electrolysis, the necessary energy input can be provided by a mixture of electrical and thermal energy. Consequently, electrochemical transformation of CO_2 can be carried out in two fundamentally different configurations: high-temperature and low-temperature methods (Endrődi et al. 2017, pp. 133–154).

High-temperature solid oxide electrolysis cells (SOECs) offer high process efficiencies in the direct electrochemical conversion of CO_2 to CO or water to H_2. Due to the high operating temperatures (750–900 °C), both the kinetics and thermodynamics of these processes are very favorable. High temperatures are needed because the electrolyte materials only become obviously ionically conductive at elevated temperatures, while the anode (usually made of metal oxides) also needs high temperatures to reach good electrical conductivity. The SOEC technology is approaching maturity, with larger pilot plants already installed worldwide (Hauch et al. 2020). This technology necessitates the application of heat-tolerant structural materials and high reaction temperatures, which results in high operational and capital investment cost. A common problem that occurs in high-temperature electrolysis is degradation and carbon deposition, resulting in shorter cell lifespan and lower efficiency. Such a system is already functioning on Mars, on the Perseverance rover, launched in 2021 (https://mars.nasa.gov/mars2020/spacecraft/instruments/moxie/; https://photojournal.jpl.nasa.gov/catalog/PIA24203). The Mars Oxygen *In Situ* Resource Utilization Experiment, or MOXIE, is small, about the size of a car battery (3.9 × 23.9 × 30.9 cm). It harvests the excess heat from an onsite radioisotope thermoelectric generator, which also provides the electric power needed for electrolysis (300 W altogether). It can produce up to 10 g O_2 per hour, and the duration will be per experiment, which will be scheduled intermittently over the duration of the mission. The aim of this experiment is to demonstrate the viability of oxygen generation for future Mars missions. This includes the oxygen needs of the astronauts, and liquid oxygen propellant for sending anything back to Earth (Figure 6.3).

While high-temperature electrolysis has certain benefits, it is limited to the generation of CO, and it needs significant heat input. At the same time, low-temperature electrolyzers can generate a wealth of other products (hydrocarbons/alcohols/formic acid, etc.) beyond CO. These chemicals can act as building blocks of functional materials (e.g. polyethylene) (Endrődi et al. 2017, pp. 133–154). Notably, water has to be transported from Earth or harvested from the crust of Mars in order to utilize the benefits of this technology on Mars. There is already a low-temperature, polyelectrolyte membrane (PEM)-based, water electrolyzer system on ISS, which employs a 28-cell stack, at a current density of 216 mA /cm^2 to produce oxygen at ambient pressure with 80% efficiency (Nelson et al. 2020). Among the low-temperature cells, two types have emerged over the years for CO_2 electrolysis: (i) microfluidic cells, in which thin liquid layer(s) flow between the electrodes, (ii) zero-gap designs, in which only the anode is fed with liquid electrolyte, but all the cell constituents are pressed together (Endrődi et al. 2017, pp. 133–154). In both cases, CO_2 is fed as a gas through a gas diffusion electrode. This technology

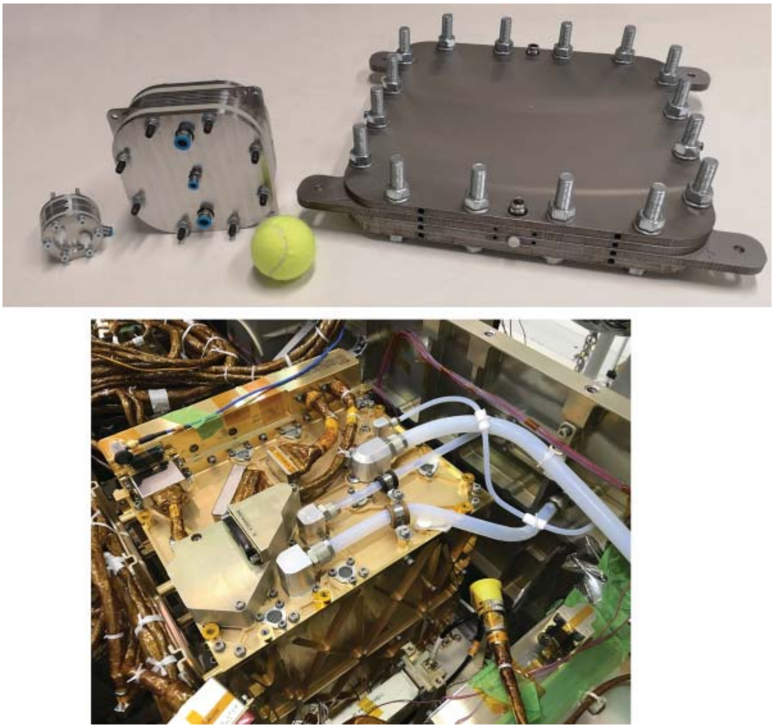


Figure 6.3 Photograph showing the MOXIE unit (NASA/JPL-Caltech) and different sized zero gap cells (from left to right: $A = 8\,\text{cm}^2$, $A = 100\,\text{cm}^2$, $A = 1000\,\text{cm}^2$) and a tennis ball having a diameter of 6.5 cm. Source: Endrődi et al. 2020, Royal Society of Chemistry.

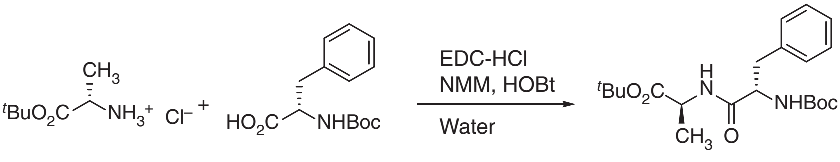
is still in the R&D phase, but larger and/or multi-layer cell stacks have already been presented to operate at sufficiently high current densities (Endrődi et al. 2020). In such configurations, one stack is made of several electrochemical cells, where the key component is a bipolar plate (acting as cathode in one cell, and anode in the subsequent cell). This approach avoids the need for manufacturing very large electrodes and cell components, and also avoids difficulties related to the management of the electrochemical process itself. Recently we have demonstrated a zero gap CO_2 cell stack, which consists of multiple layers and can operate with a pressurized CO_2 gas feed, without the need for any liquid catholyte (Endrődi et al. 2019). As a very recent development, we have shown that a key factor limiting long-term stability of low-temperature CO_2 electrolyzers is the formation of precipitates in the porous cathode from the alkaline electrolyte and the CO_2 feed. We presented that while precipitate formation is detrimental for the long-term stability, the presence of alkali metal cations at the cathode improves performance. To overcome this contradiction, we developed an operando activation and regeneration process, where the cathode of a zero-gap electrolyzer cell is periodically infused with alkali cation-containing solutions. This enables deionized water-fed electrolyzers to operate at a CO_2 reduction rate matching those using alkaline electrolytes (CO partial current density of $420 \pm 50\,\text{mA cm}^{-2}$ for over 200 hours) (Endrődi et al. 2021).

Finally, we note that beyond the obvious practical importance of this topic, there is an additional scientific aspect to be studied. It was shown in the example of water splitting that microgravity significantly influences both fluid dynamics and bubble formation, and, therefore, the kinetics of the whole process (Davenport et al. 1991; Sakuraia et al. 2013). As there is no spontaneous mixing in microgravity, it becomes crucially important to tailor the electrolyzer structure, such as the gas and liquid channels, gas diffusion layers, and catalyst layers to induce sufficient gas and liquid flow, and to ensure that the products leave the cell. Overall, there is an accelerated development in the field, and we foresee the appearance of novel technologies to be deployed in space mission soon.

6.7 Synthetic Chemistry, Purification, and Analytics in Space

6.7.1 Synthetic Efforts in Space

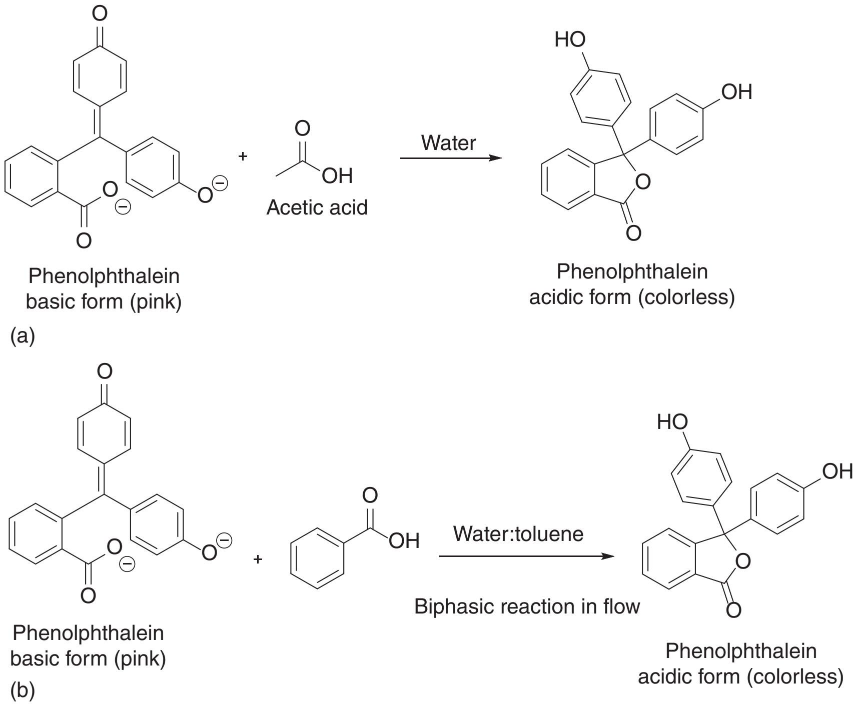
Synthetic chemistry experiments performed in microgravity environment have been scarce so far. In this chapter we discuss recent examples of synthetic chemistry in space including purification techniques and analytical aspects for space chemistry. Until recent years, performing controlled chemical syntheses in space has not been possible due to the lack of an appropriate equipment to do that. In 2019–2020, the first flow chemistry platform for synthetic reactions on the ISS was developed by the Beeler Research Group (Boston University) and Space Tango 2019 (https://www.nasa.gov/mission_pages/station/research/experiments/explorer/Investigation.html?#id=8172; Beeler 2020). Three different organic reactions were carried out inside the automated Flow Chemistry Cube Lab: a peptide coupling, a monophasic, and a biphasic colorimetric reaction. Peptides are composed of amino acids connected by peptide (amide) bonds. Peptide couplings, or more generally amide bond constructions are among the most frequently performed chemical reactions in drug discovery (Brown and Boström 2016, pp. 4443–4458). It is not surprising, therefore, that in the first experiment this reaction was investigated (Scheme 6.1). The samples from the experiment were returned to Earth and analyzed by liquid chromatography – mass spectrometry (LC–MS) and nuclear magnetic resonance (NMR) spectroscopy. The coupling reaction in this initial work gave comparable results to those obtained on Earth (Beeler 2020) indicating directional information for futures study using the automated flow-chemistry reactor system in microgravity. Reaction



Scheme 6.1 Peptide coupling reaction performed on ISS.

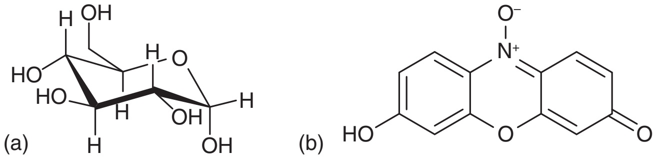
of alanine and phenylalanine in microgravity environment resulted in 85% yield and 95% mass recovery, respectively, at a residence time of three hours.

Phenolphthalein is an organic dye often used as an indicator in acid–base titrations. The compound is pink in basic solutions and turns colorless in acidic solutions. In the second experiment, a pink solution of phenolphthalein (i.e. at basic pH) was reacted with acetic acid in water to give a colorless solution at the end of the reaction (Scheme 6.2). In the third experiment, phenolphthalein was reacted with benzoic acid dissolved in toluene to afford a biphasic reaction mixture. These experiments allowed the researcher team to investigate fundamental aspects of fluid dynamics, and in particular mixing properties in microgravity environment. The outcome of the colorimetric reactions was followed by using the onboard cameras inside the Flow Chemistry Cube Lab.



Scheme 6.2 Acid–base colorimetric reactions under monophasic (a) and biphasic (b) reaction conditions performed on ISS.

In 2017, in the payload of DIDO two free orbit satellite launched by SpacePharma (www.space4p.com), the oxido-reductase catalyzed enzymatic oxidation of glucose was studied (Scheme 6.3). Resazurin was employed as an indicator and the reaction was monitored by spectrometry (https://www.space4p.com/missions). Results showed that kinetics was tenfold slower compared to ground reference, and different ratio of secondary oxidation was observed.



Scheme 6.3 Glucose (a) and resazurin dye (b).

6.7.2 Purification and Analysis in Space

Liquid separation is one of the critical steps for chemical (flow) synthesis. Liquid–liquid extractions allow chemists to separate compounds with different relative solubilities in immiscible liquids. Sufficient phase separation is thus fundamental to achieve successful extractions. Commonly liquid–liquid separations rely on sedimentation. The Zaiput (www.zaiput.com) Separator (see Section 6.8), which relies on separation based on surface tension, has been tested for continuous liquid–liquid separation on the ISS (https://www.nasa.gov/mission_pages/station/research/experiments/explorer/Investigation.html?#id=7696; https://www.zaiput.com/zaiput-in-space).

In most cases, after a reaction has taken place, the product needs to be purified. To do this, purification techniques such as extraction, crystallization, distillation, and chromatography are available for chemical practitioners and should be considered for future syntheses applications in space. Protein crystallization, as a physico-chemical formulation process (discussed in Sections 6.4 and 6.5), has been investigated in detail in microgravity environment in order to access high-quality crystals for single-crystal X-ray diffraction studies (Mohan et al. 2010; McPherson and DeLucas 2015; Strelov et al. 2014, pp. 781–806; McPherson and DeLucas 2015, pp. 1–20). Nevertheless, we are not aware of experiments utilizing crystallization as a standard purification technique in space.

Polymer research is one of the few areas of synthetic chemistry where researchers deliberately have sought microgravity conditions for three reasons: (i) microgravity greatly reduces buoyancy-driven fluid flow; (ii) the pressure head effects are virtually eliminated; and (iii) sedimentation is virtually eliminated. The possibilities of synthesizing more homogeneous polymer materials in space compared to terrestrial specimens have been discussed briefly (Downey and Pojman 2001; Briskman et al. 2001, pp. 169–180).

Thanks to its generality, in small-scale chemical drug discovery labs, column chromatography is the go-to method for compound purification. Automatic flash chromatograph systems are available for this purpose. Their footprint, however, is relatively big, and the method can generate high amount of solvent waste and significant human interaction may still be required. Therefore, it is expected to take some time and development before column chromatography becomes widely available for space applications. Focusing on the method's analytical potential instead of purification, The JET Propulsion Laboratory (JPL) (www.jpl.nasa.gov) researched and suggested microfluidics high-performance liquid chromatographic chip integrated to an ion trap mass spectrometer for answering fundamental questions in astrobiology (Kidd et al. 2015).

On-orbit analysis of chemical reactions is not straightforward, since most earth-based analytical instruments used in organic chemistry have to face a number of challenges when applied in space: besides issues originated from microgravity, the energy consumption, the large weight or size are prohibitive factors. Nevertheless, a number of analytical instruments have either been used in space or considered already for space chemistry application.

Mass spectrometers have a rich history and promising future in planetary exploration (Arevalo et al. 2019, pp. 1–17). It was NASA's Phoenix Mars Lander, equipped with a high-temperature furnace and mass spectrometer (thermal and evolved gas analyzer [TEGA]) that confirmed the existence of water ice on Mars in 2008 (Thompson 2008). The International Space Station uses mass spectrometry to monitor air quality. The so-called Spacecraft Atmosphere Monitor (SAM) is one of the smallest autonomous gas chromatograph-mass spectrometer instruments ever built, which is able to immediately detect trace contaminants that pose potential threats to crewmembers' well-being (https://www.nasa.gov/feature/nasas-spacecraft-atmosphere-monitor-goes-to-work-aboard-the-international-space-station).

NMR spectroscopy is suitable for characterizing ferromagnetic materials, thus a potential tool for analyzing samples of planets or asteroids. This technology can be operated even without containing permanent magnets by exploiting the natural magnetic fields of the mineral phases, resulting in their much lighter weight and making the technology a candidate for space research (https://www.techbriefs.com/component/content/article/tb/techbriefs/physical-sciences/6416). NMR systems and their miniaturization are intensively researched nowadays (Zalesskiy et al. 2014, pp. 5641–5694).

Spectrometers have widely been adapted for diverse space applications and have become indispensable components of space and planet exploration missions. The FTIR-based ANITA system represented a versatile air quality monitor on the ISS, allowing for the first time the detection and monitoring of trace gas dynamics, with high time resolution, in a spacecraft atmosphere (Honne et al. 2011). The CubeSat-based SpectroCube, a miniaturized *in situ* space exposure platform (Elsaesser et al. 2020, pp. 275–288), is an infrared spectrometer interfaced with a sample handling system that was designed to measure photochemical changes of organic molecules. The Mars Curiosity Rover's ChemCam fires a laser and analyzes the elemental composition of vaporized materials by an on-board spectrograph from areas smaller than 1 mm on the surface of Martian rocks and soils (https://mars.nasa.gov/msl/spacecraft/instruments/chemcam). The Perseverance Rover is equipped with Raman and fluorescence spectrometers, which upon modification should also be suitable for analysis of small organic molecules (https://mars.nasa.gov/mars2020/spacecraft/instruments). During ESA's ExoMars rover mission, a Raman laser spectrometer will investigate the mineralogical composition of powders sampled on Mars (Veneranda et al. 2020, pp. 1–14). The Microdevices Laboratory (MDL) at JPL has recently developed the "Chemical Laptop," the first battery-powered, automated, reprogrammable, portable instrument, that houses the microfluidics, electronics, and optics needed to perform highly sensitive microchip electrophoresis coupled to laser-induced fluorescence detection of organic acids and other organic biomarkers (Mora et al. 2020, pp. 12959–12966).

The establishment of flow chemical equipment for space research, in-space processing, and synthetic chemistry will evidently demand the inherent analytical tools soon, giving rapid information about the performance and/or quality of the chemical syntheses and processes realized. Although most analytical developments already validated in space have been targeted for space exploration, several of them will be applicable for tailoring to follow specific chemical processes or routes, or *in situ* analyze chemical syntheses. This means nonetheless a great challenge, considering that chemical reactions and compounds, such as of pharmaceutical production, usually requires individual methods for their reliable analysis.

6.8 Flow Instruments for Space Chemistry

6.8.1 The Flow Chemistry Advantage in Space

Flow chemistry has matured over the past two decades from early demonstrations of simple chemical transformations in microreactors to complex, multistep synthesis which are applied routinely at fine chemistry and pharmaceutical fields (Darvas et al. 2014). The technology has received a remarkable amount of attention in recent years with many reports and publications on what can be done in flow (Darvas et al. 2014; Plutschack et al. 2017, pp. 11796–11893; Luis and Garcia-Verdugo 2019; Noël and Luque, 2020). Flow chemical processes offer numerous advantages to organic synthesis over the traditional “in-a-flask” batch operation, such as assured safety, the environmentally benign green nature, shorter reaction times, excellent yields and selectivity, reduced amount of by-products and improved product quality, use of elevated reaction conditions, easy reaction control, enhanced optimization and faster scale-up opportunities, cost efficiency, and overall production flexibility. Evidently, translation of batch chemistries into continuous-flow processes is not an easy task (Akwi and Watts 2018, pp. 13894–13928).

Chemistry on Earth can thus be performed either in flasks or flow systems https://thalesnano.com/applications. This is not the case under microgravity where the solution in a flask would not mix well and reactions would not be reproducible. The emergence of flow reactors thus provided revolutionary new options to perform chemical reactions in space (Sipos et al. 2017, pp. 151–156; Mezohegyi and Darvas 2019, Hessel, et al. 2020, pp. 115774–115794). The main advantages of flow reactors vs. batch synthesis instruments in space are the following:

- ensuring efficient mixing of fluids and higher reproducibility of chemical experimentation;
- operability via complete automation and by remote control;
- ability to operate in an enhanced chemical reaction space: at high pressure and temperature which are difficult to produce by batch reactors;
- allowing reactions to be performed on very small scale, then producing a fast scale up.

In 2019, the ISS National Lab recognized that flow chemistry is an important application for future discovery and commercial efforts (https://spacetango.com/latest/space-tango-announces-iss-flow-chemistry-collaboration-with-boston-university-beeler-research-group).

6.8.2 Flow Reactors for Space Applications

It is worth to note the wide variety of flow reactor products on the market, which after appropriate modification, seem to be applicable for chemical synthesis and production in space (Figure 6.4). A simple assembly of a continuous-flow reactor includes a pump to transport the reaction reagent(s) throughout the setup and the reactor unit itself in which the chemical transformation takes place. Reactions with two or more reagents in separate streams require additional pumps to be included, as mixers to ensure efficient contact between the reagents. A chemical reaction often requires either cooling or heating in order to dissipate the excess heat or to provide energy to initiate and maintain the reaction. A back-pressure regulator is required in general to maintain a steady flow, which is critical for controlling residence times. A mass-flow controller is usually employed in flow chemistry to control the fluid flow to a set point. Inline analytics are often used to provide information about the progress of reaction performance. A detailed overview about the technology devices, configurations, and reactor solutions was given by Fekete and Glasnov (2014, pp. 95–140).

On the other hand, to design a flow reactor which is destined for operation in space is a challenging task. In practice, the fundamental aspects of constructing a flow reactor should be reconsidered. The main factors of designing a flow reactor on orbit are to define properly the material requirements of the reactor to adapt the reactor to the nature of the reactions to be performed. The pressure and temperature conditions within the reactor must follow strict safety requirements of the in-space applications. The second factor is the size of the reactors, as only limited space is available for chemical instruments brought to the orbit. The third component to be considered is the limited nature of the supplying resources such as electricity and storage volumes.

When designing the reactions in space, we should consider the material changes of the physicochemical and other processes governed by mass transfer due to microgravity (see Section 6.2). The dynamics of fluids in space is also changing relative to a terrestrial laboratory (Monti 2001). An innovative approach for flow chemistry in space is an instrument design with modular assembly. Here modules can be connected to each other in reconfigurable combinations to create a versatile chemical reactor system (Guidi et al. 2020, pp. 8910–8932). Recently, a miniaturized and modular-flow chemical reactor prototype for microgravity applications has been developed by ThalesNano (www.thalesnano.com) together with Innostudio (www.innostudio.org). The 2U-sized equipment scheduled for space qualification enables the performance of all of the important flow chemical synthesis type in a single reactor. In the down-scaled modules of the instrument, liquid–liquid reactions, photochemical/photocatalytic reactions, heterogeneous catalytic (packed-bed) transformations, and also electrochemical syntheses can be performed (Mezohegyi and Darvas 2021). Significant section of the potential on-demand syntheses of

Flow photochemistry (thalesnano.com/photocube)

Polar Bear Plus-Flow Synthesiser (cambridgereactordesign.com)

Labtrix- Microchip reactor (chemtrix.com)

Asia Syringe Pump (syrris.com)

FlowSyn (uniqsis.com)

H-Cubehydrogenation (thalesnano.com)

FlowCAT (helgroup.com)

Scale-up flow chemistry (thsenergy.com)

Advanced-Flow Reactors (corning.com)

Figure 6.4 Examples of flow chemical reactors available on the market.

organic chemicals in space is expected to be covered by the modular prototype. Its chemical performance under microgravity, including the synthesis of a world top API, and testing of the reactor will be targeted on ESA’s Space Rider (https://www.esa.int/Enabling_Support/Space_Transportation/Space_Rider) maiden flight, the researchers stated (Mezohegyi and Darvas 2021).

The first systematic approach to perform systematic organic synthesis experiments in space by using flow reactors was made by the Beeler research group (https://www

.beelerlab.com/research.html) in 2020. Partnering Space Tango (www.spacetango.com), the team investigated three fully automated chemical reactions on the ISS and made the first effort to synthesize organic compounds onboard (Beeler 2020). The sealed 9U tool was equipped with cameras, pumps, flow meters, pressure sensors, and sophisticated valving to ensure safe and efficient operation. The flow system was capable of ensuring a reaction temperature between 4 and 100 °C, a flow rate between 0.25 and 2.0 ml /min, and also end-product capture (Stoudemire 2020). The reactor, developed by the Beeler group, at its size of 8.0 cm × 5.5 cm, had a useful volume of 1 ml. The reactions included peptide coupling and a water-phase colorimetric reaction (synthesis of phenolphthalein) (see details in Section 6.7).

Today, the scientific and commercial opportunities via flow chemical equipment and applications in space research and space industry are getting more and more clear. Among others, the ICE Cubes Service (www.icecubesservice.com), available in the Columbus module of ISS, is a capable experiment platform offering to host a wide range of experiments such as reaction for drug discovery, organ-on-a-chip, cell biology, protein crystallization, 3D tissue engineering, additive manufacturing, nanoparticles etc. An extension of the platform by a multi-user chemistry platform in the near future is being considered, which will include also a flow chemistry module, among others (Stenuit et al. 2021).

6.9 Conclusions

Space chemistry is a fast-emerging novel field, already with some important applications in the pharmaceutical industry. It is expected that versatile flow reactors operating in space will open new avenues to establish novel synthetic routes to existing drugs and new reaction classes leading to unusual chemical structures.

On the other hand, as our chapter demonstrates systematic studies of indigenous synthetic opportunities offered exclusively by space have yet to be started. The reasons are multiple: theoretical chemistry should more precisely pinpoint the unique synthetic opportunities which will be available exclusively in space; on instrumental side, synthesis, purification, and analysis should be provided by complex and compact instruments. A louder voice expressing the need for breakthrough results to the multiple important unsolved industrial problems will definitely stimulate further efforts of space chemistry on orbit.

Nevertheless, the space chemistry community believes that the versatile flow reactors under development will open new avenues to many fields in chemistry to the practical benefit of humankind on Earth.

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