Pure & Appl. Chem., Vol. 60, No. 11, pp. 1669–1678, 1988.
Printed in Great Britain.

Automation in the organic chemistry laboratory: Why ? How ?

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Abstract - Except in the analytical laboratories, there has not been until very recently a development in the use of automatic systems in chemistry laboratories comparable to what has been observed in the production units (or even in the field of electrical domestic appliances). However, experience has shown that the equipment of a research or development chemistry laboratory with more or less complex automatic systems significantly improves the efficiency of the researchers' and technicians' work on the condition, of course, that they simultaneously receive an adapted training. Indeed, not only the observations increase in number and in quality, security and working conditions are improved, but moreover, chemists experience a renewed interest in their activities which then become free of any repetitive and tedious aspects. The purpose of this paper is to focus attention on the difficulties which must be overcome in order to offer organic chemists automatic systems which correspond to their needs.

1. INTRODUCTION

In 1966, MERRIFIELD (1) proposed the first apparatus for automatically synthesizing oligopeptides. Since this pioneer work, much progress has been achieved in automation in general and automation of laboratory operations in particular (2-9). This progress has gone hand in hand with the astounding progress of electronics and data processing, to such an extent that the electromechanical systems initially designed (1,2) bear no relation to the computerized systems available today (10-12).

Despite these highly spectacular advances, one has to admit that the speed and extent of penetration of automatic systems in chemical laboratories varies considerably with the individual firm and type of activity. In particular, one is obliged to admit that automatic systems are set up much faster in our kitchens than in our organic synthesis laboratories !

What are therefore the reasons explaining this lag ? Can anything be done about it ? First of all why develop installation of automatic systems in organic synthesis laboratories ? These are the questions we should strive to find an answer to in this brief paper.

2. IMPACT OF AUTOMATION IN CHEMISTY LABORATORIES

Before describing the interest of automatic systems that can be used in organic synthesis laboratories and the conditions for setting them up to ensure optimum use, it seems necessary to make a number of distinctions.

Due to differences in the nature and quantities of the products involved and the methods used, there are in fact wide differences between organic chemistry laboratories, mineral chemistry laboratories, physical chemistry laboratories and analytical chemistry laboratories. For instance, analysis work generally involves small quantities of products and is often repetitive in nature, which is why such work lends itself well to automation. Accordingly, it is not surprising that automatic systems were quickly set up in analysis laboratories during the last 20 years, and did not encounter any reluctance from the analysts, who were very happy to be relieved of repetitive and tedious tasks.

In the case of organic synthesis laboratories, the situation is more complicated, since we can in fact distinguish:

- fundamental or applied research laboratories that are typified by the wide diversity of the tests performed and the small quantities of reagents used,

- development laboratories within which tests are less varied but generally involve larger quantities.

However, this distinction does not sufficiently allow for the nature of the activities of chemists in their laboratories. Indeed, in a research laboratory, albeit fundamental, the chemist may have to prepare relatively large amounts of the raw materials he will need.

Three types of tests can then be distinguished, depending on their end-purpose:

- exploratory tests,
- confirmatory tests,
- optimization tests.

The purpose of the exploratory tests is more or less systematic exploration of an experimental field in order to reveal a new reaction or more generally a new chemical phenomenon. These tests are generally carried out in large numbers and involve using small quantities of reactants (0.1 to 1 g).

During the confirmation stage, the purpose of the tests is to determine the conditions of observation of the chemical phenomenon discovered during the exploratory stage. These tests generally involve quantities of from 1 to 100 g.

Lastly, the optimization tests enable the experimental conditions to be determined for instance enabling a reaction to take place with the greatest possible efficiency or the products expected to be obtained with the highest possible level of purity.

As can be seen, these various research stages can be differentiated more particularly:

- by the scope of the experimental area explored,
- by the quantities of products involved and hence the size of the reactors,
- by the number of tests.

The automation equipment proposed to chemists must allow as much as possible for these specificities.

3. WHY AUTOMATE OPERATIONS IN THE ORGANIC SYNTHESIS LABORATORY?

3.1 To improve the quality of the observations and the reproducibility of the results

Whereas it is difficult for a chemist to watch more than two parameters at a time and act simultaneously on several control devices of these parameters, automatic devices can measure, record and control a practically unlimited number of parameters. With such devices, it is now possible to separate the functions of measurement, decision-making and action. This is why, far from being deprived of their abilities to observe as some still claim today, on the contrary, the abilities of observation and intervention of chemists are considerably enhanced when they use well designed automatic systems.

Use of such devices also enables the accuracy and reproducibility of results of experiments conducted under conditions of better control to be improved, which is particularly interesting for optimization studies which in most cases required an experimental plan. The results of these experiments obviously cannot be exploited unless they are reproducible. The improvement to the quality of measurements brought about by automatic systems is sometimes such that the chemist gains access to new reaction parameters. For instance, a reactor initially designed for carrying out synthesis operations automatically enables calorimetric measurements to be made. (10)

3.2 To improve the working conditions of chemists

Use of automatic systems relieves the chemist of repetitive and tedious tasks thus enabling him to manage his time better. This is why he can give more time to in-depth use of the results he obtains and conceives new experiments. The time savings also give him better control of the ever increasing information he receives, be it chemical or other wise and not forgetting administrative tasks which alas, show no tendency to diminish.

3.3 To improve safety

Provided the automatic systems are well designed, well installed and well maintained, correct use enables the safety of the chemists and the laboratories to be increased.

They in fact enable the risk of human error due to lack of attention, lassitude and fatigue to be eliminated. Equally, they enable the possible consequences of explosions or release of toxic products to be reduced. These risks can be eliminated if the automatic systems are remote-controlled in a suitably isolated chamber.

Likewise, automatic systems enable the overall level of safety to be enhanced, since use of such systems requires the chemist to carry out prior analysis of the risks that can occur at all stages in the experiments, which is by no means not the least of their advantages.

3.4 To increase the productivity of research and creativity of chemists

In the light of what has just been described, clearly, the improvement to research productivity related to the use of automatic systems is not only quantitative in nature. To be sure, provided the safety conditions are complied with, the number of tests can be increased by using these systems without the presence of chemists. Primarily, however, one must stress the need to improve research productivity qualitatively, through better definition of the experimental conditions, reproducibility of the results and improvement to the intellectual and material working conditions of the principal people involved in research, namely the chemists. With these new tools at their disposal and provided they are well mastered, chemists are more free to use their imagination and explore new experimental fields, which very often results in an appreciable enhancement of their creativity.

4. HOW CAN ONE AUTOMATE OPERATIONS IN THE ORGANIC SYNTHESIS LABORATORY?

4.1 Specifications, an indispensable item

Regardless of the type of tests to which it is desired to apply automatic systems, it is indispensible to define the objectives that one intends to reach by means of these systems as precisely as possible and then to select the means enabling these objectives to be obtained with the greatest care.

These are *two essential stages in the approach to setting up automatic systems (moreover*, not only in an organic synthesis laboratory but in any other environment). These stages must be the occasion for the widest and deepest possible concertation between future users and the designers of automatic systems (or the specialists responsible for acquiring these systems).

At each of these two stages of the project to set up automatic systems, a document should be drawn up:

- <u>the functional specification</u> must specify the objectives and performances desired from the system,

- <u>the organic specification</u> must define the equipment to be used to achieve these objectives.

The quality of the thinking "invested" when drawing up these documents is the major factor governing the final success of the project. Only too often, the user is tempted to save time in these stages and choose the system and its elements on the basis of insufficiently accurate or objective criteria, leading to serious difficulties later and the risk of being discouraged from continuing *the experiment attempted on automation*.

4.1.1 *Functional specification*

The following should be specified in this document:

- the nature and quantities of the products to be involved,

- the physico-chemical characteristics of these products and in particular their corrosivity and the hazards they may give rise to,

- the operations that are to be performed,

- all the physical and physico-chemical parameters that will have to be measured and/or controlled, defining the required accuracies and measuring ranges,

- the functions to be provided:

  . types of regulation,

  . nature of automatic systems (combinatory, sequential...),

  . control mode of systems,

  . recording (and) processing of results,

  . nature of alarms and safeties to be provided, depending on whether the system is to be operated with or without surveillance,

  . possibilities of taking over control manually.

To describe the operations desired and their sequencing, it is convenient to use symbols understandable at one and the same time by the chemist and the automation specialist. Chemists appreciate the simplicity of logic flowchart type diagrams, whilst automation specialists prefer the relay or GRAFCET language. Very probably, the development of use of microcomputers as control devices will bring these conflicting standpoints closer together.

Let us briefly examine a few major points concerning the functions we wish to achieve.

TYPES OF REGULATING SYSTEM

The most widely used method of regulation in organic synthesis laboratories still remains the very simple "all or nothing" mode, which is very often sufficiently efficient for small installations. However, the reduction in the sizes (and costs) of "Proportional, Integral and Drift" (PID) regulation systems now enables them to be used in laboratory apparatus, especially for temperature control.

Certain PID regulators are now self-adjusting and even self-adapting, endowing them with considerable simplicity and flexibility of use and they are tending to become more and more widely used in laboratories and pilot units.

NATURE OF AUTOMATIC SYSTEMS

Combinatory automatic systems enable one or several actuators to be controlled in the light of the values of the parameters and settings given to them by the operator during a single sequence of operations.

Sequential automatic systems enable several sequences to be strung together, between which the nature and/or values of the parameters controlled can be modified.

SYSTEM OPERATING MODE

The operating mode for automatic systems can be brought about in several ways:

- in the distributed or "local" operating mode, the settings and controls are made from elements each fulfilling one regulating function (determination of settings of power to actuators, etc...),

- in the "centralized" operating mode, the settings and controls are made from a central unit which is now a microcomputer. Control is then possible directly via a keyboard/screen or through a programme stored on floppy disk.

Hybrid modes also exist endowed with some of the characteristics of each of the modes briefly described above.

RECORDING AND PROCESSING OF THE RESULTS

This consists of recording the different parameters of the reaction or even the nature and duration of the actions either using a graphic recorder with one or several channels for systems with distributed architecture, or by using the possibilities of storage and display offered by a microcomputer which monitors a system with a centralized structure.

In the latter event, the computing power of the microcomputer makes it very simple to process the results obtained during the operations, rendering their use and storage particularly easy (we see here the rise of veritable computerized laboratory logs).

NATURE OF ALARMS AND SAFETIES

The purpose of these systems is to foresee and/or eliminate the dangers that any unexpected event in the reaction or any failure of an automation system could lead to for personnel and the laboratory.

Safety is active if the corresponding devices can intervene on all the parameters on the basis of the signals put out by detectors dedicated to maintaining safety.
The alarms (not active) can correspond to the parameters controlled, in which case the regulator could have two adjustable alarm thresholds (low and high). Alarms may also correspond to unregulated parameters monitored by dedicated sensors triggering an audio or luminous signal, though not leading to any action.

POSSIBILITIES OF TAKING OVER CONTROL MANUALLY

It is indispensible to be able to intervene directly on an automatic laboratory system in order to interrupt or modify operations. These operations must be arranged so that they can be conducted under satisfactory conditions of safety both for the operator and his environment. This implies not only a well-designed system, but also excellent knowledge of the system by the user.

4.1.2 *Organic specification*

When all the important points of the functional specification have the widest possible agreement between future users, one must then draw up the organic specification corresponding to the system projected. The purpose of this document is to arrive at the best possible compromise between the performances of the system and the objectives defined in the functional specification.

The organic specification is the concrete outcome of choices covering:

- the type of equipment,

- the system architecture,

- the constituent parts of this system,

so that the objectives are achieved under the best possible conditions of efficiency, safety and cost.

TYPES OF SYSTEMS

Two main types of equipment for automating operations in the organic synthesis laboratory exist:

- modular equipment (3, 13)

- integrated equipment (10-12)

Some of these equipment units may offer the characteristics of each of the two types at one and the same time.

At present, modular equipment is preponderant. Such equipment is formed from packages each ensuring one (or two) functions corresponding to measurement, action or control through appropriate sensors and actuators. These systems enable flexible and open-ended units to be formed, so that the capital investment required can be brought together gradually. So as to be reliable, these systems must be built with the greatest care using high quality components. Particularly close attention must be given to the problem of systems for linking together different packages.

The integrated systems combine into the same unit devices enabling information concerning the automated process to be acquired and action on devices for controlling the actuators.

These automatic systems are generally designed to carry out a single type of operation or a series of repetitive operations. For instance, the organic chemist now has available:

- laboratory reaction (or fermenting) vessels

- peptide synthesizers

- oligonucleotide synthesizers

- distillation apparatus

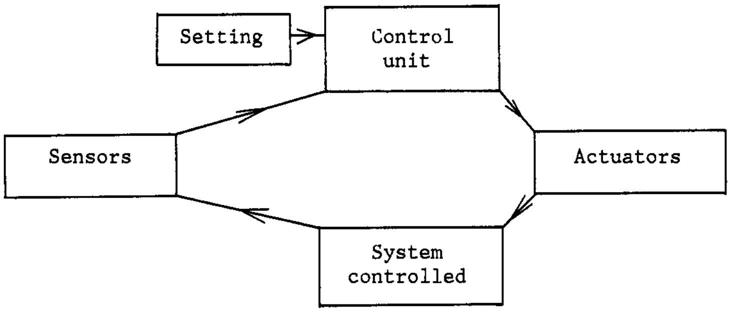
- extraction devices

Systems of this type are generally more rugged than modular systems. Provided they are well designed, application can be extremely simple and requires only minimum training. However, by the very fact of their design, these systems are inflexible, considerably limiting their range of use. Accordingly, it is generally not possible to vary the volume or shape of a reaction vessel within an integrated system. In addition, the number of parameters that can be measured is set in the design and modification may lead to modifying the system programme. For some time, thanks to the development of more flexible and open-ended control software, the integrated systems now proposed allow a certain degree of flexibility in the choice of certain elements and endows them with some of the advantages offered by modular systems in this field.

ACTUATORS

Actuators are the elements of an automatic system acting on the system controlled so that it is maintained in the state desired or changes from one state towards another under well-defined conditions.

Actuators are applied by the control unit on the basis of the indications of the sensors, with the information running in an "automation loop" in accordance with the following flowchart:



In this paper, it would be impossible to review, albeit rapidly, the very wide variety of actuators that may be used in automatic systems on the scale of the laboratory. The main types of operations relate to :

- energy transfers:
  - heating,
  - cooling,
  - stirring,
- transfer of matter:
  - gaseous,
  - liquid,
  - solid.

Time control should be added to these operations, since this is clearly an essential parameter for the chemist.

In the majority of cases, all these operations are carried out by electrical devices:

- resistances (heating),

- motors (stirrers, pumps, compressors...),

- electromagnets (electrovalves),

- radiating devices: infrared, ultraviolet, ultrasonics (14) and very recently microwaves (15).

The actions can be performed by pneumatic devices (turbines, valves and cylinders), that are electrically controlled.

For a number of years now, a new type of actuator has appeared in laboratories, namely manipulating arms, commonly (though abusively!) known as robots. These systems enable samplers, reagents, small reactors to be transferred between a number of weighing, processing (agitation, heating, spinning...) and analysis (chromatographs, spectrometers, titrometers...) systems. Up till now, these systems have primarily been used in biochemical and pharmacological laboratories and in particular analysis laboratories. Recently FUCHS (16) has shown the possibility of using these systems to carry out a series of operations involving organic synthesis : weighing and loading of reagents, transfer into agitated and heated (or cooled) reactors, sampling for analysis of samples during reactions and processing of reaction mixtures. It appears that it is particularly advantageous to use these manipulating arms for exploratory tests and it is certain that equipment specifically intended for this use will increase.

In order to be part of an automated laboratory system, actuators must be endowed with a number of qualities that are difficult to reconcile. Before all else, such actuators must be reliable, in other words their operation must be both highly certain and highly reproducible. The care taken in designing and building them must make them highly robust, both mechanically and electrically. They must be capable of withstanding corrosive atmospheres and solvent vapours present in the fume cupboard of organic chemistry laboratories.

Should the actuators be placed in an atmosphere containing high concentrations of solvent vapours, it is naturally preferable to use explosion-proof apparatus, though the overall dimensions and high cost of this type of apparatus in fact cause it to be used only rarely. The simplest solution generally consists in maintaining the entire apparatus under strong ventilation currents in order to prevent combustive vapours from gathering. When there is still a risk of explosion, pneumatic actuators must then be used.

SENSORS

Clearly, temperature is the most important parameter that must be measured and controlled during organic synthesis and existing sensors (thermocouples, platinum resistance probes) generally prove entirely satisfactory.

Nor does control of pressure or vacuum set any real problems, since the relevant sensors (deformable membrane gauges or sensors, resistance gauges) are reliable and easy to use.

By developing accurate, rugged and reliable weighing systems (scales, tippers, strain gauges), the organic chemist can now continuously weigh solid, liquid or gaseous reagents that he has introduced (or even the entire reaction vessel !).

In particular, gas flows are easy to measure by mass flowmeters, though on the other hand low liquid flows are still somewhat delicate and progress still has to be made in this field.

Despite the progress of catalysis by phase transfer or electrosynthesis, only few organic reactions take place in an aqueous medium, so electrochemical probes (pH, pE, conductivity meter probes...) are used only little by organic chemists. However, it should be remembered that it is not indispensible to use an aqueous solvent to observe electrochemical phenomena. Such phenomena can result from "events" that occur during the reaction and on which one can zeroing for optimization.

CONTROL UNITS

Reference to the above diagram shows that the control unit receives the information from the sensors, compares this information against the settings made by the operator (or stored in a programme) and deduces from it the signal to be sent to the actuators so that the operation or sequence of operations takes place as intended. This is the central function of the control unit.

Initially, this function was given to simple relays enabling the logic signal generated by the system comparing the value measured by a single sensor to a single setting value to be converted into a control signal for a single actuator. In order to combine a number of logic signals obtained from several detectors and control several actuators in accordance with a well determined logic process, one of the following devices can be used:

- logic correlator,

- programmable controller,

- microcomputer.

Already proposed in 1968 by LEGRAND (3), the logic correlator enables signals from sensors and comparators to be combined in highly simple fashion by means of AND, OR or NOR logic gates. The resultant signals are applied to the actuators through power relays supplying them. Its very considerable simplicity and ruggedness are the main advantages of this system, the performances of which however are very limited, since it only enables a single sequence of operations to be programmed, applying a limited number of sensors and actuators. Nonetheless, it still remains highly useful and is a particularly efficient pedagogical tool for teaching chemists Boolean algebra and elementary programming.

To control complex laboratory operations or to conduct sequences of operations, the chemist has available either programmable controllers or microcomputers. About 10 years ago, the distinction between the two types of hardware was very clear-cut. Today, this difference is tending to become less clear. Industrial programmable controllers are units intended to control repetitive industrial operations, mostly in the electrotechnical or mechanical area. To be able to use them, the chemist must learn the fairly simple programming language, though one that is relatively specific to the programmable controllers, and how to link these units together with the laboratory sensors and actuators. This operation is relatively easy, since through their design, the automats have devices enabling them to be linked with the sensors (inputs) and actuators (outputs).

Once these obstacles have been overcome, programmable controllers become powerful tools for carrying out automated operations and are highly robust and highly reliable (17). Furthermore, in most cases, their modular design enables them to be used readily in systems of variable complexity.

Since their advent about 10 years ago, microcomputers have undergone extraordinary evolution with repercussions in every sector of human activity. The activity of organic chemists is no exception. Not only does the microcomputer permit word processing, storing of results, access to data banks, molecular modelling and assistance in the conception of organic synthesis, but also enables the chemist readily to control automated systems.

The reason for this is that the extraordinary computing and storage power of the microcomputer can be used to:

- decode the signals from the sensors,

- compare them to the settings in a programme that can be highly complex,

- determine the actions that should be carried out so that the programme takes place as intended,

- store all the information,

- process this information making it readily and immediately accessible to the chemist,

- make all the necessary computations,

- display the results on a screen or print them out on a printer.

To conduct these operations, the user has more or less high level programming languages. The systems provided to chemists for several years are particularly simple to apply. The user programmes the operation desired by answering the questions of a "menu" that is displayed on the screen to specify the parameters of the operations and to programme their sequencing.

Successful system performance stems not only from the development of these particularly user-friendly complex programmes but also the existence of systems enabling the sensors and actuators to be conveniently linked to the microcomputer. These interfacing problems, that were only until recently still one of the disadvantages of microcomputers with comparison to programmable controllers, are now a thing of the past. Only the relative fragility of microcomputers (in particular their mass memory: floppy disks, hard disks and their drives) continue to set real problems, that should be borne well in mind when choosing a control system. If a microcomputer is selected, it is absolutely vital to provide suitable protection against the corrosive atmosphere of organic chemistry laboratories.

EXCELLENT QUALITY CONNECTION SYSTEMS

Whether automatic systems are integrated or modular, it is highly important to see that the quality of the connectors and cables interconnecting the different constituents of the system be of top quality.

Experience in fact proves that most of the failures of automated laboratory systems arise from defects or wear in the connecting systems.

The wear of these systems obviously takes place faster (hence increasing the probability of failures) for modular systems and in this case, particularly close attention must be paid. The connectors must be capable of withstanding multiple assembly/disassembly operations and the cables of withstanding the corrosive atmosphere of laboratory fume cupboards.

The necessary ability to withstand the environment of a research laboratory is not the only problem set by the connecting systems. The multiplicity of the cables, their intermingling and dimensions rapidly become a hindrance as the complexity of the systems built by modular automatic systems increases. This is a real problem, to which no solution has been found for the moment, though infrared or even optical fibre connecting systems might be one. Such systems are already used in everyday life (control of television sets or magnetoscopes by infrared, telecommunications via optical fibres), though they have not yet entered organic synthesis laboratories.

4.2 Need for suitable training (or: how can the robots 'tame' the chemists?)

It is not sufficient to design and build high performance and reliable automated systems, one must also ensure that the organic chemists agree to use them and use them properly. This is not the least difficulty involved.

Whilst chemists are amenable to all innovations concerning reagents, reactions and catalysts that they are led to discover through their research, they often consider with the greatest mistrust the devices proposed to them to automate laboratory operations. Indeed, they fear that these devices move them further away from the chemical events they wish to observe and make it more difficult to survey and control the reactions studied. In fact, as we saw earlier, none of this is true and well designed automatic devices on the contrary increase the observing capabilities of chemists tenfold. However, they still have to be convinced ! This is the function of training, which must necessarily precede and accompany the setting-up of automated laboratory systems.

During their scholastic studies and subsequently their career, organic chemists indeed rarely acquire the training enabling them to make suitable use of automated laboratory systems. Accordingly, they should be offered suitably adapted training in this field. The main elements of this training can be divided into three stages :

- training in the use of simple modular systems,

- training in the use of programmable controllers,

- training in the use of microcomputer-controlled systems.

Broken down in this way, training is progressive and hence less forbidding.

During each session, particular stress must be laid on the importance of choosing the sensors and actuators in any laboratory apparatus (automatic or not !). All new-comers indeed attach too much importance to the control/monitoring systems, forgetting that the characteristics and reliability of an automatic system are never better than those of its weakest element. Indeed, of what importance is it to have a highly sophisticated microcomputer and control software if the overall operation depends on a poorly adapted or calibrated sensor or an insufficiently powerful actuator ?.

Naturally, this type of training must include much practical work enabling the chemist to apply the principles acquired during theoretical lessons and preferably to familiarize himself with the automatic systems he will be using in his laboratory.

Our experience, gained over the last ten years, shows that after the first 35 hours session, chemists are convinced of the advantages of modular automatic systems for their work and are capable without difficulty of building and suitably applying corresponding systems for common organic syntheses. Once this step has been achieved, many manifest the wish to go further and increase their theoretical and practical knowledge in this field and follow a more specialized or higher level course.

4.3 Maintenance

As the reader has already been reminded, the electronic and data processing systems used in organic synthesis laboratories may be subjected to solvent vapours or corrosive gases. Not only is it important to design them in such a way that they can withstand this type of environment as best possible, but it is also indispensable to take the greatest care in maintaining them. Preventive maintenance will ensure that the mechanical, electrical and electronic characteristics are maintained and that performance still meets the initial specifications. With this in view, it is particularly indispensable to carry out routine checking of the connectors and recalibrate the sensors. Repair of failed or damaged equipment (curative maintenance) must be entrusted either to the maker of the equipment or to competent specialists.

4.4. Safety

Correct use of well-designed automatic equipment by well-trained chemists as well as regular maintenance of the equipment are all safety factors. However, the complexity of certain systems is sometimes such that it may be necessary to back up intrinsic safety systems with alarm and safety devices enabling a system to be monitored in a completely independent fashion, thus limiting the risks in the event of an operating system failure.

The training for users of automatic laboratory systems must comprise at least one session on the specific safety problems set by using automatic devices.

5. PROSPECTS

As we hope to have shown, organic chemists now have available reliable and high performance equipment for conducting organic synthesis operations under better conditions of safety and efficiency. Setting up these systems in laboratories can be beneficial only if it is carried out in compliance with the precautions we have briefly set forth in this paper. Under these conditions, the evolution of the work of the chemist will be such that it is no exageration to say that we shall see the rise of a new trade involving not only knowledge of chemistry, but also the control of the new tools we have been discussing.

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