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Automated Synthesis: Development of a New Apparatus Friendly to Synthetic Chemists (MEDLEY)

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Abstract:

A new type of automated synthesizer has been developed on which a variety of synthetic reactions can be conducted. Since the apparatus is completely sealed, reactions which require an inert atmosphere are feasible without difficulty. The reaction temperature is changeable from the temperature of dry ice to room temperature. The temperature is controlled within ±0.1 °C. The amount of reagents added is accurate within ±0.01 mL. With the advanced control function, the process time is minimized. Thus, the apparatus is particularly convenient for running multifold reactions sequentially.

Introduction

The automation of synthetic manipulations is of great importance from both economical and ecological points of view. In fact, the full automation has been realized in industrial chemical plants, as it is rather easy to realize automation in commercial plants where the routine operations are repeated on a large scale. On the other hand, the bench work still remains far behind such innovation despite increasing demands for high efficiency and reliability in laboratory operations as well as for facilities to produce pharmaceuticals and speciality chemicals on a relatively small scale. The experimental techniques for synthetic reactions have experienced virtually no improvement for a long time in contrast to the outstanding progress in analytical instrumentation. The reason for such delay in innovation is as follows. (1) In laboratories, various types of reactions must be employed, and thus, the apparatus must be designed for multipurpose uses. The design of the apparatus is therefore much more complicated than that for the apparatus for specialized use in commercial plants. (2) Small-scale operations encounter technical difficulties in various aspects. For instance, many organic reactions should be run under a rigorously inert atmosphere, but it is rather difficult to completely seal the apparatus from ambient air in small-scale reactions. Also, it is not easy to weigh and charge small amounts of reagents with high precision. Despite these difficulties, there are some synthetic machines which are available for commercial or for in-house use.[1] However, most of them are designed towards optimization of reaction parameters, and hence, less attention has been paid to dealing with air-sensitive or thermally labile compounds. More seriously, they are not suitable for treating consecutive reactions because only a single reaction usually can be run in one reactor.

Two strategies are feasible for automation of the multistep process. One is so-called "robotics", a miniature of industrial plants, in which the intermediate products are automatically transferred from one reactor to another. This system, however, could be expensive to build, and air-sensitive or thermally labile substances cannot be readily transferred from flask to flask in laboratory-scale operations. The other is a one-pot process where manifold reactions are consecutively conducted in a single reactor. We report here a new type of automated synthesizer which allows reactions under the same reaction conditions as those employed by synthetic chemists in normal bench work. In particular, a series of reactions can be connected sequentially in one reactor.

Results and Discussion

Figure 1 illustrates the diagram of our automated synthesizer. The apparatus is basically composed of a control unit (automatic reaction system (ARS)[2] and a sequencer[3]), a glass reactor, reservoirs, volumetric pumps,[4] a syringe for quenching the reaction, and a cooling unit. ARS controls the whole system and is linked to the valveless piston pumps to regulate the rate of reagent addition via the sequencer. Each pump is equipped with a ceramic piston rod and a cylinder, both of which are tolerant to a variety of acidic and basic reagents to be charged. The pumps, equipped with a valveless piston system, enable precise loading of liquid materials. The ceramic piston rod is connected eccentrically to a rotor as depicted in Figure 2. This distortion between the axes of the rotor and the piston rod allows the piston rod to undergo reciprocating motion in the cylinder upon the revolving of the rotor. It follows that during one complete revolution, the piston executes just one stroke. The piston rod has a slot, and the piston itself can serve as a control valve so as to regularly switch introduction and release of the liquid materials. As shown in Figure 3, when the piston

(1) For recent reviews: (a) Lindsey, J. S. *Chemom. Intell. Lab. Syst.* **1992**, *17*, 15. (b) Sugawara, T.; Cork, D. G. *Lab. Rob. Autom.* **1996**, *8*, 221. (c) Harre, M.; Tilstam, U.; Weinmann, H.; *Org. Process Res. Dev.* **1999**, *3*, 304.

(2) ARS (Automatic Reaction System) is an automatic reaction controller commercially available from Sogo Pharmaceutical Co., Ltd., Tokyo. ARS is equipped with sensors for monitoring the temperatures of reaction mixture and methanol coolant. It also determines electric currents for driving the pumps to load reagents as well as the pump to circulate the cold methanol, according to the programmed reaction temperature. The feedback circuit is running constantly on ARS so that the rate of reagent loading could be maximized by balancing the pump powers for both reagent loading and methanol circulation.

(3) The sequencer is originally designed and constructed by Sogo Pharmaceutical Co., Ltd., Tokyo for multistep reactions. In the sequencer, the drivers of pumps and memories for input of the order and the amount of reagents are incorporated.

(4) The volumetric pumps and drivers are commercially available from Yamazen Corporation, Tokyo.

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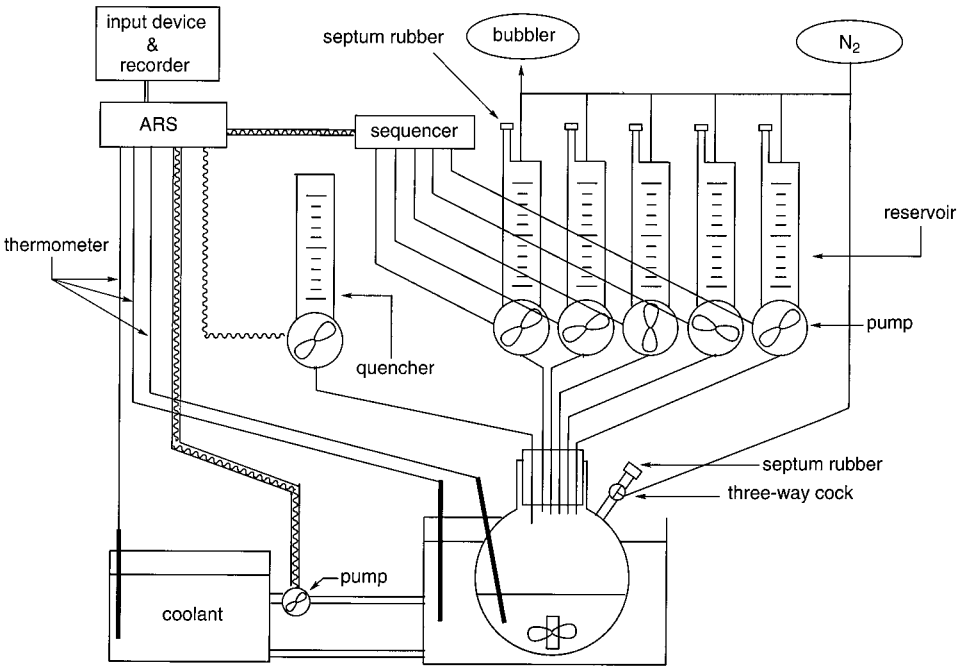

Figure 1. **Schematic diagram of MEDLEY.**

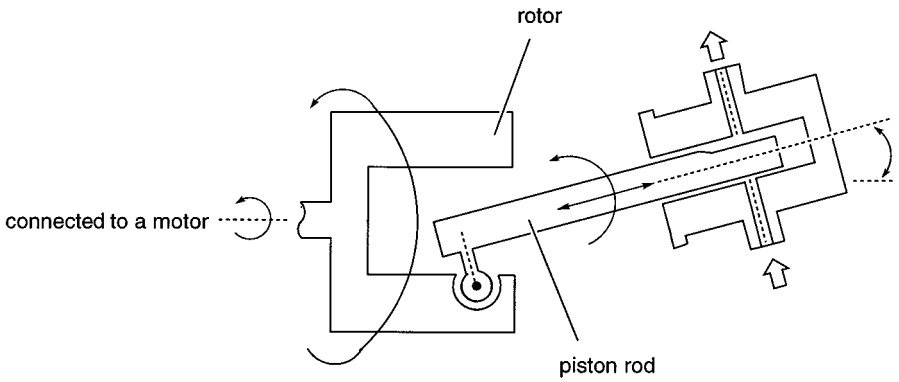

Figure 2. **Cross section of the volumetric pump.**

goes down, the rod opens an injection port to introduce the liquid into the cylinder while an exhaust port being shut. Conversely, upon rising, the rod closes the injection port and opens the exhaust port to press out the liquid. With the use of such a mechanism, the amount of added reagents is volumetrically quantified with deviation less than ±0.01 mL.

Reagents are kept in the reservoirs, and both the volume and the order of reagent addition are programmed into the sequencer. The programs for the temperature and for the operations throughout the process are input into ARS. The addition rate is adjusted by ARS so as to maintain the programmed reaction temperature. The reaction temperature is controlled by changing the flow rate of the coolant to be accurate within ±0.1 °C by way of the feedback circuit from the three sensors; one immersed into the reaction solution directly, the second into the coolant running in the jacket of the reaction vessel, and the third into the coolant kept in the refrigerator, respectively. The order of reagent addition is programmed into the sequencer connected to ARS, which is equipped with an advanced control function that can initiate the next task immediately after the previous one has finished so that the processing time can be minimized.[5] With this technology in hand, we can conduct sequential reactions in a practical manner by charging various reagents one after

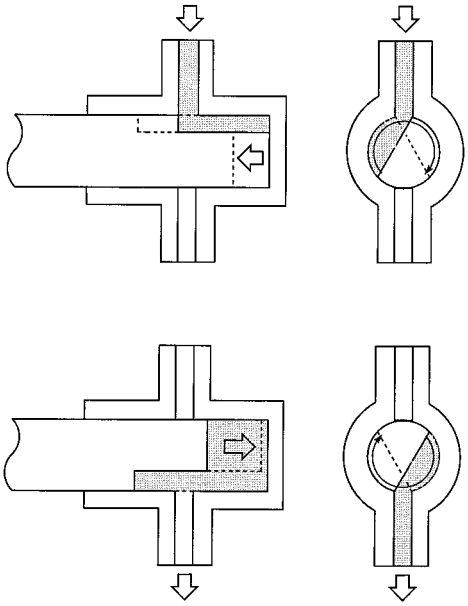

Figure 3. **Cross section of the valveless piston system.**

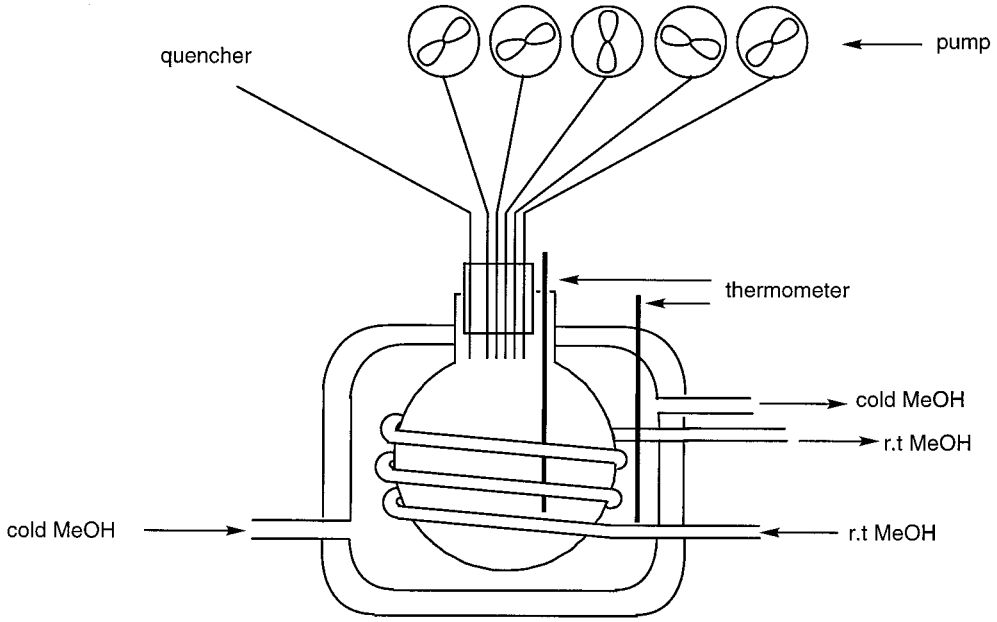

Figure 4. **Cross section of the reactor.**

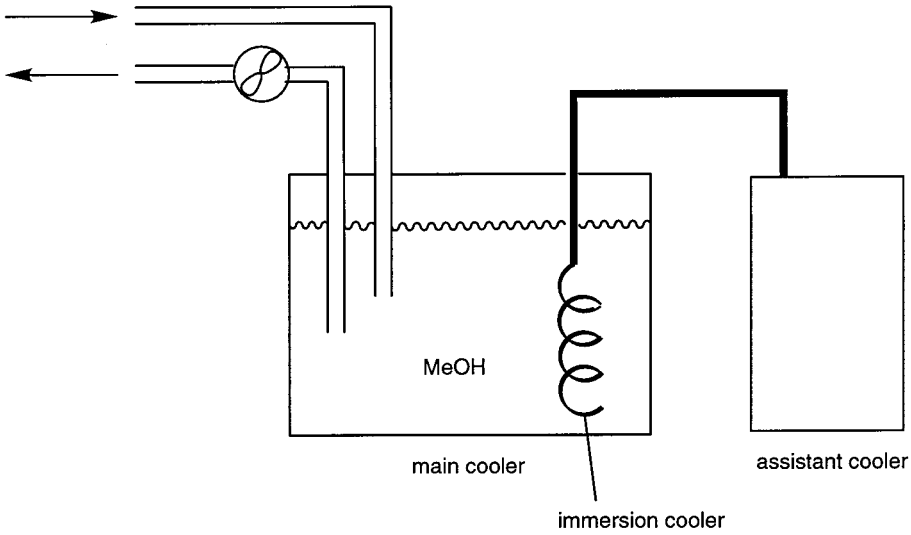

Figure 5. **Schematic diagram of the cooling unit.**

another. Thus, we designate our apparatus as MEDLEY which is named after the medley relay of a swimming race where different swimming styles are relayed in succession.

The reactor has a three-layered structure (Figure 4): the outermost layer is the vacuum temperature insulator, the cold MeOH circulates in the second layer, and the innermost reaction flask is jacketed by a glass tube through which warm (usually room temperature) MeOH flows. By balancing the currents of both cold and warm MeOH, the reaction temperature can be tuned very quickly. For instance, the temperature is warmed from −74 to 20 °C within 5 min, while it is cooled from room temperature to −74 °C within 10 min. This is very convenient to carry out the sequential reactions which proceed at different temperatures. At present, we have two reactors which are different in size, 50 mL and 130 mL, respectively.

When all processes have finished, ARS sends an ending signal to the controller of the quenching system. The quencher syringe contains a quenching material which is usually water but could be other ones if necessary. The controller, upon receiving the signal, starts to put the quenching material into the reactor.

In general, the reaction temperature of −30 °C can be reached easily by a commercial refrigerator, but reactions below this temperature are difficult to run with most automated synthesizers. However, the reaction at low tem-

(5) The reaction temperature is highly influenced by the ambient temperature and humidity. Thus, repetition of identical reactions directed by even the same reaction program resulted in varied reaction periods when each task was programmed in terms of the time. In these operations, therefore, we need to set long performance times to fully secure the completeness of the tasks. Thus, we constructed a time-independent control function which can initiate the next task immediately after completion of the preceding one. This control system is also highly useful to overcome "overnight stirring problem" which causes troubles on occasion in the process development. As pointed out in an article by Stinson, S. C. in *Chem. Eng. News* **1999** *77*, 35, synthetic chemists frequently leave reactions to run overnight simply because of their convenience; yet it may happen that this is too long and gives rise to a worse outcome than it might be actually.

perature, especially at dry ice temperature, is indispensable in organic synthesis. This has been realized in our apparatus by connecting two air-cooled refrigerators (Figure 5).[6] A complementary immersion cooler works to support the main refrigerator, and the pump attached to the main refrigerator is driven by ARS so as to maintain the programmed temperature.

Finally, it should be noted that the inside of the apparatus is completely sealed. All reservoirs and the reactor have two inlets. One is a reagent inlet which is capped with a rubber septum, and the other is a gas inlet connected to a flow line of inert gas. Teflon tubes attached to the outlets of the pumps are fixed through a rubber septum of the reactor. All of the connection points are reinforced with an agglutinant. Evacuation followed by refilling with nitrogen or argon provides an inert atmosphere at the same level as that which synthetic chemists usually employ in bench work.

(6) Our cooling system consists of main and complementary refrigerators commercially available from Thomas Kagaku Co., Ltd., both of which can remove the heat of 350 kcal h^{-1} under maximum power.

In conclusion, an automated synthesizer has been developed which enables to conduct manifold reactions sequentially under the conditions that are employed in usual synthetic reactions. MEDLEY has not yet been installed in the workup and analysis units. We did not lay the priority on these technologies at the first stage of this project because technical problems for these goals have been fully cleared already.[1c,7] The utilization of the apparatus in synthetic processes will be described in the following paper.

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