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A Simple Low- to Medium-Pressure Hydrogenation Manifold

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Abstract:

A hydrogenation/reactive gas manifold designed for rapid screening of a wide range of reaction conditions on limited amounts of material is described. The manifold delivers reactive gas to four independent reactor ports, each equipped with inerting, pressurizing, and venting valves, as well as thermocouple capability. Magnetic stirring and bath/mantle temperature control are used in the individual reactions; the reaction vessels are available in a wide range of sizes. Delivery of different pressures of reactive gas to the individual reactions is enabled by insertion of in-line regulators between ports. The modular nature of the design allows additional reaction ports to be added as needed. The manifold accommodates reaction pressures of up to 60 psig.

The need to accommodate a recurring research situation has often been the driving force for development of new chemical techniques, technology, and equipment. Such was recently the case when we were required to rapidly evaluate an array of catalysts and conditions for a hydrogenation step in the synthesis of a clinical candidate. Our need to evaluate the parameters for the reaction was further constrained by limited amounts of the requisite synthetic intermediate, a situation frequently encountered in the early stages of synthetic development. We found the commercially available options (atmospheric/balloon hydrogenation, pressure bottles, autoclaves, shakers) to be cumbersome or inadequate for our needs, and we sought to develop technology to address our situation.[1] In this Technology Report we detail our solution, an easily assembled low- to medium-pressure hydrogenation/reactive gas manifold with wide versatility, which we believe will be of general interest to laboratories needing to practice hydrogenations on small to moderate scales.

In our design considerations, we sought to include maximum flexibility in the manifold design, incorporating the ability to vary as many parameters in the reactions as possible, coupled with ease of use and flexibility in construction of the manifold itself. Thus we envisioned a hydrogenation/reactive gas system which would deliver the gas to several reactor ports, with each port having independent inerting, pressurizing, purging, and sampling capability. Reaction vessels with reasonable pressure ratings (50−60 psig) and size ranges would be desirable. Magnetic stirring and bath/mantle temperature control were deemed advantageous. Finally, the manifold would have some level of portability, so that it could be used communally among laboratories on an as-needed basis in an individual fume hood.

Our prototype manifold is shown in Figure 1. Constructed of $^1/_4$ in. stainless steel tubing and joined with standard fittings, the manifold combines a line for inert gas or vacuum (A), a line for the reactive gas (B), and a pressure relief valve set at 60 psig (C).[2]

Connections to the inert gas source (at point E) and reactive gas source (at point F) are made with thick-walled flexible plastic hose (rated to 209 psig[3]). We employ in-house nitrogen as our inert gas source, delivering it to the manifold at about 12 psig. The reactive gas is delivered from a lecture bottle source.

The modular nature of the independent reactor ports is evident from inspection of Figure 1. In theory the manifold can be built to include as many ports as desired, since in construction each individual port is added on to the manifold via $^1/_4$ in. spacing tubing (D) in the reactive and vacuum/inert gas lines. We employ a four-port design, representing for us the best combination of number of reaction ports and ability to use the manifold in one half of a conventional fume hood. Spacing between ports of about 10−11 in. comfortably allows room for individual magnetic stirring. We support the manifold by anchoring it with clamps to a rigid grid of stainless steel rods. This enhances portability and helps minimize setup time, as one simply clamps the manifold grid to the existing grid in the hood.

An individual port detail is shown in Figure 2. The three-valve system for inerting (A), pressurizing with reactive gas (B), and venting (C) as shown allows for independent operation to enable sampling, removal, etc. We employ commercially-available reaction vessels constructed of thick-

(1) We are aware of several in-house approaches to this type of problem, one of which has been disclosed; see: Seif, L. S.; Dickman, D. A.; Konopacki, D. B.; Macri, B. S. *Catalysis of Organic Reactions*; Kosak, J. R., Johnson, T. A., Eds.; Marcel Dekker: New York, 1994.

(2) Standard valves, tube fittings, and connections available from the Swagelok Company, Solon, OH, were used in construction. See supporting information for additional details.

(3) Available from Cole-Parmer Instrument Co., Chicago, IL, and Ace Glass, Inc.

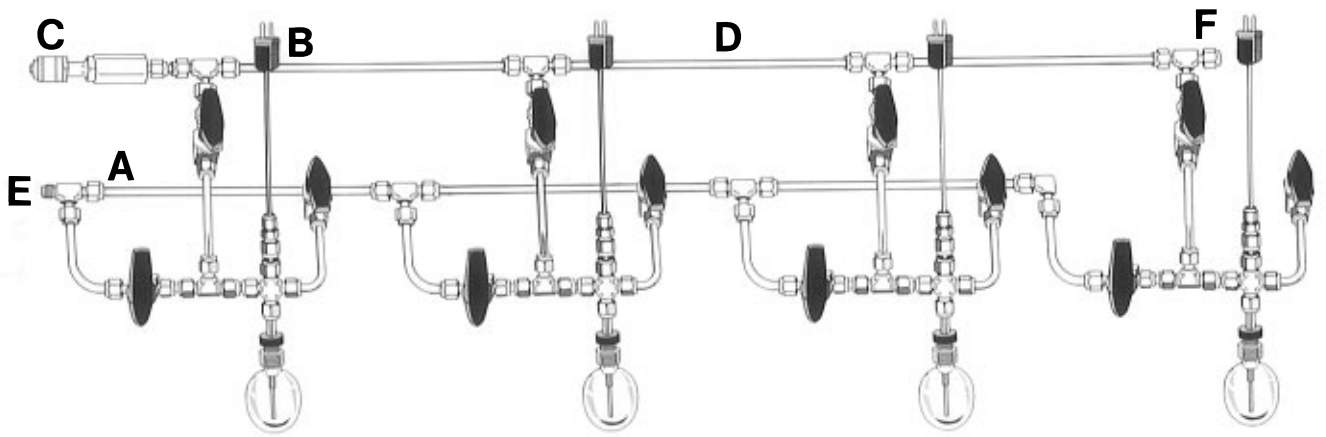

Figure 1. **Four-port manifold: (A) inert gas/vacuum line; (B) reactive gas line; (C) pressure relief valve; (D) spacer tubing; (E) inert gas connection point; (F) reactive gas connection point.**

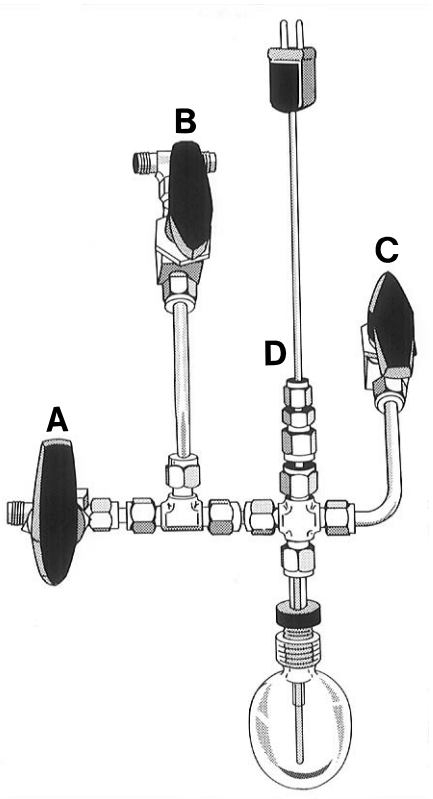

Figure 2. **Individual reactor port detail: (A) inert gas/vacuum valve; (B) reactive gas valve; (C) vent valve; (D) thermocouple port.**

walled glass designed for running smaller scale shaker hydrogenations; they are pressure tested to 150 psig and recommended for use up to 60 psig and 80 °C.[4] Reactor working volumes of 1 mL to 1 L are available. Connection is again made via thick-walled plastic tubing. The vessels have screw-on tops that enable pressure-tight seals with O-rings or poly(tetrafluoroethylene) (PTFE) sleeves. A thermocouple port (D) is incorporated to allow internal temperature monitoring; we employ a thermocouple, temperature control system and heating mantle to run reactions above room temperature. The thermocouple port may be capped off with the appropriate fitting if not needed.

The manifold delivers reactive gas to all ports at the pressure specified at the source. To enable variation of this

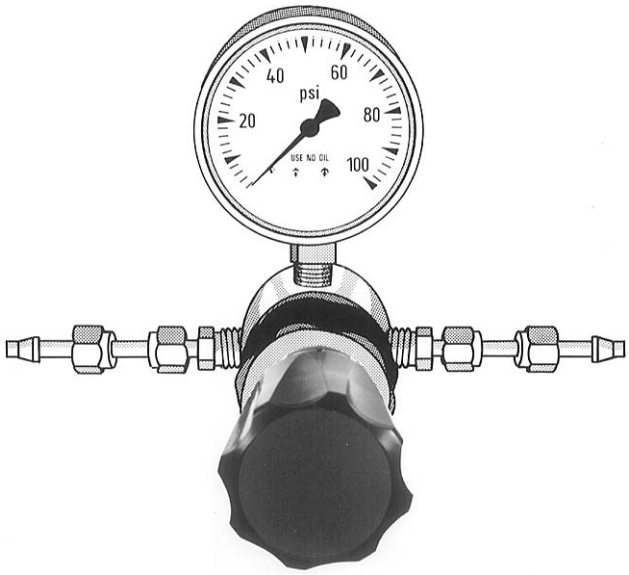

Figure 3. **In-line pressure regulator assembly.**

parameter, in-line pressure regulators can be inserted easily between all or some of the reactor ports. Thus replacement of the reactive gas stainless steel spacing tubing (D, Figure 1) with an in-line pressure regulator and accompanying connections, as detailed in Figure 3, allows different pressures to be applied to various reactor ports. In our design, reactive gas is delivered from the right-hand side of the manifold; an in-line regulator will thus specify the pressure delivered to ports to the left of its location. By replacing all reactive gas spacing tubing with in-line regulator assemblies, differential pressures can be applied to all ports in the manifold, from the highest pressure, at the far right, to the lowest pressure at the left end of the manifold. The in-line regulator selected[5] has 316 stainless steel and PTFE construction and can withstand conventional oil pump pressures on its outlet side.

Because of the low dead volume in the manifold, inerting and pressurizing are remarkably quick operations. Provided that the plastic tubing inlet to the reaction vessel is located high enough above the solution surface, bumping or foaming into the manifold is not a problem. In practice, we run the

(4) Available from Ace Glass, Inc., Vineland, NJ; 1996 Catalog, pp 195–197.

(5) Available from Air Products, Inc., Allentown, PA. We thank Dr. Barry Jacobson (Ricerca, Inc.) for this suggestion.

pressurized reactions with a shaker-type safety screen in place.[6] The manifold at present delivers reactive gas to all ports without the capability of measuring gas uptake in a given reaction. For our purposes this feature did not appear critical for a general purpose portable manifold for screening of reaction conditions, although adaptations to the manifold as presented here to accommodate this feature should be possible. Reaction progress is monitored by analyzing reaction aliquots, taken after depressurizing the individual reaction vessel and disconnecting it from the manifold. Construction of the four-port manifold from the available components was accomplished in about 1 day.

Using the manifold, we have run several hydrogen-based reactions, including reductions of aromatic nitro groups, nitrile reductions in ammoniacal ethanol, aromatic ring dehalogenations, simple double-bond reductions, and reductive cleavage of nitrogen−oxygen bonds. The materials of construction of the manifold should allow for a range of other reactive gases to be employed; compatibility can be checked with any standard source for material compatibility with chemical reagents.[7] We note here that the manifold as constructed is compatible with carbon monoxide, syngas (CO/H_2) mix, ammonia and alkylamine gases, and hydrogen.

The ready availability of the materials of construction provides general access to this manifold, while flexibility in its modular design enables its adaptation to most laboratory situations. The ability to run several small-scale reactive gas reactions under varying conditions of solvent, temperature, and catalyst at low to moderate pressures, coupled with portability and ease of use, makes this manifold an attractive alternative to existing technology.

Supporting Information Available

Exploded view diagram of Figure 2 and complete parts list and ordering information for four-port manifold (2 pages). See any current masthead page for ordering and Internet access instructions.

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(6) Available from Parr Instrument Co., Moline, IL, and Ace Glass, Inc.
(7) See, for example: Schweitzer, P. A. *Corrosion Resistance Tables*, 3rd ed.; Marcel Dekker: New York, 1991.

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1997.