Michigan, for assistance in arranging a student-exchange fellowship for D.M.H.

Registry No. 1, 952-92-1; **2a**, 14258-07-2; **2b**, 66875-56-7; **3a**, 18624-74-3; **3b**, 34881-63-5; **3c**, 71964-42-6; **3d**, 34881-67-9; **3e**, 71964-44-8; **3f**, 71964-46-0; **3g**, 34881-68-0; **3h**, 71964-47-1; **3i**, 71964-49-3; **3j**, 21529-82-8; **3k**, 10504-64-0; **3l**, 24806-62-0; **3m**, 22900-27-2; **3n**, 1763-99-1; **3o**, 71964-50-6; **3p**, 15390-22-4; **3q**, 59395-08-3; **4** BF_4^-, 67659-43-2; **4** ClO_4^-, 59348-51-5; **5**, 14258-07-2; **6a**, 71964-51-7; **6b**, 21101-77-9; **8a**, 59395-04-9; **8b**, 59395-06-1; **9**, 108-88-3; **10**, 766-92-7; **11**, $R^2 = CH_3S$, 7451-74-3; **14**, 59395-09-4; **15**, 875-30-9; **16**, 71964-52-8; **20**, 1145-26-2; 1-methyl-3,5-bis(methoxycarbonyl)pyridinium perchlorate, 39246-18-9; 1-methyl-3,5-bis(methoxycarbonyl)-1,2-dihydropyridine, 66875-59-0; *dl*-methionine methyl ester, 43189-32-8; phenacylphenylmethylsulfonium perchlorate, 38178-48-2; $C_6H_5COCH_3$, 98-86-2; $3\text{-}CH_3OC_6H_4COCH_3$, 586-37-8; $4\text{-}NO_2C_6H_4COCH_3$, 100-19-6; $3\text{-}NO_2C_6H_4COCH_3$, 121-89-1; CH_3COCH_3, 67-64-1; CH_4, 74-82-8; $CH_2(CN)_2$, 109-77-3; CH_3SCH_3, 75-18-3; $CH_3SC_6H_5$, 100-68-5; $C_6H_5SC_6H_5$, 139-66-2; $BrCH_2COC_6H_5$, 70-11-1; $BrCH(CN)_2$, 1885-22-9; 4-methoxyphenacyl bromide, 2632-13-5; 3-methoxyphenacyl bromide, 5000-65-7; 2-methoxyphenacyl bromide, 31949-21-0; 4-nitrophenacyl bromide, 99-81-0; 3-nitrophenacyl bromide, 2227-64-7; 2-nitrophenacyl bromide, 6851-99-6; methyl fluorosulfonate, 421-20-5; benzyl bromide, 100-39-0; phenacyl phenyl sulfide, 16222-10-9; iodoacetic acid methyl ester, 5199-50-8; *dl*-methionine, 59-51-8.

Notes

Vacuum Liquid Chromatography: An Alternative to Common Chromatographic Methods

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There is a constant need in organic chemistry to separate both large and small quantities of mixtures efficiently, rapidly, and inexpensively. Unfortunately, it is seldom that all three of these requirements are satisfied in the commonly used chromatographic techniques. Efforts to improve these methods include the use of multibore columns,[1] flash chromatography,[2] automated systems,[3] and dry-column chromatography.[4] We wish to report the development of vacuum liquid chromatography (VLC), a method which we feel possesses all of the desirable characteristics mentioned above. VLC has become the major method for separation of steroids and marine natural products in our laboratory.

The development of this method arose from the need to have a simple inexpensive chromatographic system at the bench, capable of producing good resolution in a short time. A previous attempt to achieve this goal utilized a sintered-glass Büchner funnel, partially filled with TLC grade sorbent, under vacuum as a "column".[5,6] This afforded resolution comparable to that of gravity column chromatography (70–230 mesh sorbent) but in a much shorter time period. The major drawbacks to this very simple system were channeling, caused by the necessary intermittent breaking of the vacuum, uneven sample application, and limited resolution due to the shortness of the column. VLC overcomes these drawbacks.

Channeling was eliminated by developing a system in which the column was kept under vacuum continuously. Sample application problems were overcome by (a) decreasing the ratio of column cross section to the quantity of the sorbent (use of a longer, narrower column) and (b) by the use of a preabsorbent layer of celite such as that used on some TLC plates. Resolution was increased greatly by an increase in column length relative to cross-sectional area.

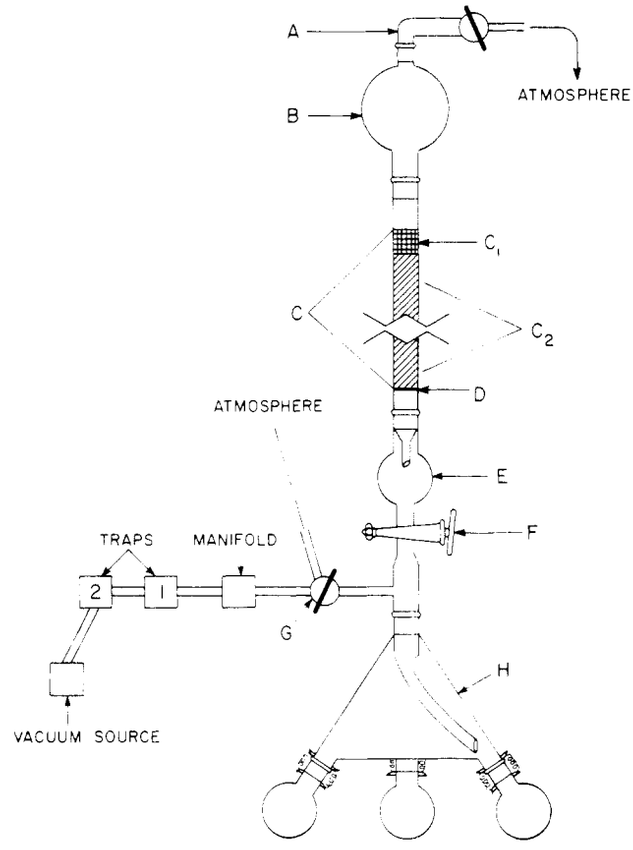

Figure 1. VLC apparatus and some specifications: A, stopcock/stopper; B, solvent reservoir (2 L); C, column; C_1, preabsorbent layer (diatomaceous earth, celite, filter aid or equivalent); C_2, sorbent (TLC grade, 10–40 μm); D, sintered glass frit (10–20 μm pore size); E, eluent reservoir (250 mL); F, column isolation stopcock; G, vacuum/atmosphere stopcock; H, receiver head; trap 1, 250 mL; trap 2, 50 mL; vacuum, mechanical pump.

The apparatus shown in Figure 1 consists of the column C fitted with standard taper joints at upper and lower ends

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(2) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
(3) W. H. Pirkle and R. W. Anderson, *J. Org. Chem.*, **39**, 3901 (1974).
(4) B. Loev and M. Goodman, *Chem. Ind. (London)*, 2026 (1967).
(5) B. F. Bowden, J. C. Coll, S. J. Mitchell, and G. J. Stokie, *Aust. J. Chem.*, **31**, 1303 (1978).
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and a fritted disk D to retain the sorbent. The collection section of the equipment consists of a bulb E in which eluent can be stored while flasks are replaced in the "cow" section H. The collection section is connected to the vacuum source by way of the usual stopcocks and traps.

Although most column chromatographic methods utilize wet slurry methods of packing, we have found that for VLC a vacuum dry-pack method gives the best results. This technique affords a much greater sorbent density than dry gravity packing and avoids channeling which is frequently encountered in the slurry–vacuum method. A further desirable compacting of the column is achieved by closing the upper stopcock A and then opening it suddenly to the atmosphere. A preabsorbent layer of celite is also added by the dry-pack method in an amount one tenth by weight of the sorbent. This layer not only protects the surface of the sorbent but, because of its weak adsorptive power, ensures that the sample moves onto the column with the solvent front as a uniform narrow band.

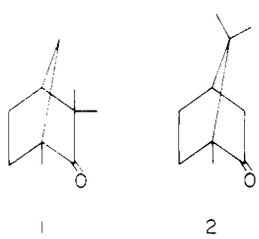
The fact that the system is under vacuum raises questions concerning solvent volatility, not only with respect to loss of solvent in the collection section, but also with respect to bubble formation in the column itself which would disrupt column flow. This problem apparently caused the early discarding of vacuum techniques as alluded to in earlier books.[7] Using the design and method of operation described in the Experimental Section, we found that solvent loss was surprisingly small even for volatile solvents, and cooling of the collection flasks is unnecessary. In addition, column disruption due to bubble formation has not been encountered. This result is achieved by maintenance of only the minimum vacuum required for adequate solvent flow.

To prevent solvent from entering the mechanical pump, two traps (250 and 50 mL capacities) are present, both of which can be easily isolated from the rest of the system (Figure 1). Both are cooled in Dewar flasks with a dry ice/acetone mixture. The traps need be emptied only when using highly volatile solvents or long running periods.

Flow rates observed with the system vary, depending upon the pressure, amount of sorbent, solvent viscosity, column dimensions, and sample properties. Table I lists some observed rates at constant pressure and may be used as a guide for elution rates of solvents with both high and low viscosity. Obviously, low solvent viscosity and large column diameter facilitate elution.

The resolution obtained by VLC is comparable to that obtained by TLC. As an example, "Baker's TLC reagent" [dimethyl yellow, R_f ($CHCl_3$) 0.59; indophenol blue, R_f 0.50; sudan red G, R_f 0.39] which cannot be separated by gravity column chromatography (silica, 70–230 mesh) is easily separated by VLC (silica, 10–40 μm, $CHCl_3$). Visual separation of the dyes is achieved in the top 2 cm of the sorbent.

To test the system on a preparative scale, 1 g of a 1:1 mixture of *d*-fenchone (1) and *d*-camphor (2) was quantitatively separated on 50 g of silica (32 × 140 mm column, 10–40 μm, 1% EtOAc/99% petroleum ether eluent) in approximately 2 h with at least 50 mL of pure solvent collected in the eluate between the two compounds. Stahl[8] found a R_f difference of only 0.05 on silica gel TLC plates eluted with $CHCl_3$. In test runs of VLC using more polar solvents (5 and 10% EtOAc in petroleum ether), the separation was not as complete, giving slight overlap of fractions. These results were attained without visual, UV, or refractive index (RI) monitoring of the immediate eluent.



1 2

As with all other column chromatographic methods, a wall effect is observed in which the sample migrates faster at the outer edges of the column. This was minimized in difficultly separable mixtures by application of the sample to the center of the preabsorbent layer (see Experimental Section. Sample Application B). It was also possible to minimize the wall effect by jacketing the column with an ice/water slurry. This increased the viscosity of the solvent at the glass-sorbent interface, slowing the migration at the outer edges of the column.

The only drawback to the VLC method is the inability to use UV or RI detection systems. On the other hand, in contrast to low-pressure techniques, solvent manipulation can be achieved at will because the top of the column is at atmospheric pressure. In addition, extensive tests on identical columns showed that separation of material was at least twice as efficient using the VLC method as it was using slurry or dry packed[2] low pressure columns.

In summary, VLC allows the rapid and very efficient separation of mixtures with a resolution comparable to TLC, in a simple and inexpensive apparatus, which can be manufactured in any laboratory.

Experimental Section

VLC is a liquid chromatographic technique utilizing reduced pressure to increase the flow rate of the mobile phase. The operating pressure in general is ~1–10 mmHg, achieved by means of a mechanical vacuum pump. All joints are size 29/42, and the glassware, tubing, stopcocks, etc., are of sufficient quality to function under vacuum (Figure 1). The sorbents are E. Merck products.

Column Packing. A vacuum dry-pack method is used. Stopper A and reservoir B are removed, the sorbent (10–40 μm) is poured into the column (C) and allowed to settle by gravity with manual tapping to eliminate any major air pockets. Stopper A is placed with the stopcock closed directly over the column (C), and the entire system is evacuated, allowing the compression of the sorbent. This is again aided by manual tapping. After the compression of the sorbent by the vacuum is complete, stopcock F is closed, and the stopcock on stopper A is opened. This sudden return of the column (C) to atmospheric pressure compresses the sorbent further. With the system under vacuum (stopcock F opened, stopper A removed), the top layer of the sorbent is then further compressed manually, using a flexible metal rod fitted on one end with a cork, Teflon, or rubber stopper. The total compression of the sorbent when compared to gravity packing is approximately 30–35% by volume. Stopcock F is now closed, and a preabsorbent layer of diatomaceous earth (~10% of the weight of the sorbent) is added on top of the sorbent and compressed manually as described above.

Sample Application A. The sample is dissolved in the selected eluent and applied all at once to the preabsorbent layer. The tendency here is to use too little solvent since work with preabsorbent layers of this type is not common. As an example, when a 1-g sample is applied to a 40 mm diameter column, 5–10 mL of solution is usually minimal to ensure even distribution. For best sample application, a small flask containing the sample solution is inverted quickly onto the column. The solution is

(7) E. and M. Lederer, "Chromatography", Elsevier, Amsterdam, 1957; T. I. Williams, "Introduction to Chromatography", Blackie & Son, London, 1946.

(8) E. Stahl, "Thin-Layer Chromatography", Elsevier, Amsterdam, 1957.

Table I. Flow Rates at 2.5 mmHg through Silica[a] and Preabsorbent[b]

solvent	wt of silica, g	column width, mm	column ht, mm[c]	flow rate, mL/min
petroleum ether[d]	50	32	140	5
CCl_4[e]	50	32	140	2.5
petroleum ether	25	32	70	10
CCl_4	25	32	70	4
petroleum ether	10	10	18	0.8
CCl_4	10	10	18	0.3
petroleum ether	5	10	8.5	1.1
CCl_4	5	10	8.5	0.5

[a] 10-40 μm. [b] Diatomaceous earth-weight preabsorbent is 10% that of the silica. [c] Height of sorbent only. [d] Viscosity (20 °C) = 0.3 cP. [e] Viscosity (20 °C) = 0.97 cP.

allowed to be absorbed by the preabsorbent layer (C_1), and with the system under vacuum, successive small volumes of solvent are added until the resulting narrow sample band is introduced onto the sorbent (C_2). Although best avoided, the preabsorbent and the top of the absorbent layer may run dry during sample application without adversely affecting the column. Once the sample is on the sorbent, the column and solvent reservoir can be filled with solvent as desired.

Sample Application B. For difficult separations, a glass tube having a diameter of approximately half that of the column is inserted into a one-hole rubber stopper, and one end of the tube is carefully forced through the preabsorbent layer (C_1) until contact with the sorbent is made. Diatomaceous earth is then added through the tube and compressed manually to produce a layer twice the height of the original preabsorbent layer. With the rubber stopper securely in place on the top of the column, the sample, dissolved in a minimal quantity of solvent, is applied through the glass tube, using the same method as that described in procedure A. When the narrowed sample band is on the sorbent, the glass tube is cautiously removed.

Elution. Elution is performed under vacuum. The vacuum is applied to the system until the solvent front has passed through the length of the sorbent. Stopcock G is then closed to eliminate direct exposure of the eluent to the vacuum system. To maintain a constant solvent flow rate and vacuum, stopcock G need only to be opened for short, intermittent periods (e.g., ~30 s every 5–10 min). Stopcock F is closed, affording minimal loss of eluent during these evacuation periods, and the eluent is collected in the reservoir (E) during this time. It is convenient to perform this evacuation procedure while changing fractions by rotation of the receiver head (H).

When collection flasks are filled, they are easily replaced after isolation of the receiving unit from the system. The manifold and stopcock F are closed (i.e., eluent is collected in reservoir E). The receiving unit is brought to normal pressure by the opening of stopcock G to the atmosphere. After the flasks are changed, the manifold and stopcock G are opened to the vacuum, which results in the evacuation of the receiving unit. Once the receiving unit is at sufficiently low pressure, stopcock F is opened, and the elution is continued, as described. Since the collected fractions can be evaporated quickly under reduced pressure and transferred to other flasks, only six or nine ground-glass flasks are needed for operation of the system.

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Catalytic Reactions of Pyridine with CO and H_2O. Reduction of CO to Hydrocarbon. Applications of the Water-Gas Shift Reaction. 4[1]

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We are currently searching for homogeneous metal-cluster catalysis reactions which mimic heterogeneous catalysis reactions. In this regard, we have recently described the rhodium cluster catalyzed exchange of deuterium for hydrogen at the saturated carbons of triethylamine, which occurs concurrently with rhodium catalysis of the water–gas shift reaction.[2] This observation coupled with our continuing interest in catalysis reactions wherein H_2O serves as the source of hydrogen[1-3] prompted the investigation of a possible catalytic reaction of pyridine with CO and H_2O under conditions where homogeneous catalysis of the water–gas shift reaction is known to occur.[4]

Under the conditions described below, pyridine reacts via several pathways to give products resulting from reduction, hydrodenitrogenation, methylation, and aminomethylation.[5]

Experimental Section

General Methods. Pyridine was purchased from Baker (100.0% purity, confirmed by NMR, GC, and GC/MS) and 2-, 3-, and 4-methylpiperidine, piperidine, 2-, 3-, and 4-methylpyridine, and 2-, 3-, and 4-formylpyridine was purchased from Aldrich. $RH_6(CO)_{16}$ was purchased from Strem Chemicals and CO from Matheson Gases. All reagents were used as received.

Product Analysis. Initial product analysis was performed by using a gas chromatograph–mass spectrometer (LKB-9000 interfaced with a PDP-12) equipped with a 40-m OV-101 capillary column. Products were identified by 70-eV fragmentation patterns, and elemental composition was confirmed by high-resolution mass spectrometry using a CEC21-110B instrument. Further confirmation was obtained by enhancing production of an identified product as described below and comparing 70-eV mass spectral fragmentation patterns of the proposed product with that of enhanced product as well as by comparing retention times on the GC/MS capillary column and the retention times of the products on a 4.0 m × 0.328 cm column packed with 5% carbowax on acid-washed Chromosorb G installed in a Hewlett-Packard Model 5711 gas chromatograph equipped with FID. ^{13}C NMR spectra were taken on an XL-100-15FT spectrometer modified for multinuclear operation. Me_4Si was used as internal standard.

Catalytic Runs. A standard run for the pyridine study requires mixing 6.0 mL (74 mmol) of pyridine, 2.0 mL (110 mmol) of H_2O, 0.1 mmol of $Rh_6(CO)_{16}$, and 1.5 mmol of *n*-butyl ether (internal standard for GC analysis) in a quartz-lined Parr general-purpose bomb reactor. The reactor, which contains the mixture and a magnetic stir bar, was sealed and degassed by three 800-psi pressurization/depressurization cycles with CO. The reactor is then charged to 800 psi of CO and heated with stirring at 150 °C for 5 h. After 5 h, the reactor is quickly cooled to 0

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(2) R. M. Laine, D. W. Thomas, L. W. Cary, and S. E. Buttrill, *J. Am. Chem. Soc.*, **100**, 6527 (1978).
(3) R. M. Laine, *J. Am. Chem. Soc.*, **100**, 6451 (1978).
(4) Some work in this area has previously been reported: N. S. Imyanitov, B. E. Kuvaev and D. M. Rudkovskii, *Zh. Prikl. Khim.*, (*Leningrad*), **40**, 2821 (1967). However, under the conditions reported it is possible to hydrogenate pyridine with CO and H_2O without catalyst as described by Dr. Frank R. Mayo of this research group: *J. Org. Chem.*, 1, 496, (1936).
(5) For a description of aminomethylation, see A. F. M. Iqbal, *Helv. Chim. Acta*, **54**, 1440 (1971), and references therein.

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