Fully Automated Workstation for Liquid−Liquid Equilibrium Measurements

Boris Kuzmanović,* Mathijs L. van Delden, Norbert J. M. Kuipers, and André B. de Haan

Separation Technology Group, Faculty of Chemical Technology, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands

A fully automated workstation has been developed and applied to the measurement of liquid−liquid equilibrium. The measurements, starting from solution preparations through equilibrium establishment and chemical analysis of both phases and ending with the determined solute concentration in both phases, can be done on a 24 h per day basis with no human intervention at all. To evaluate the accuracy of the measurements, the equilibrium distribution ratios of acetone between toluene and water at 20 °C and of caprolactam between toluene and water at 40 °C and between benzene and water at 20 °C are measured and the results are compared with the values reported in the literature and, for the caprolactam systems, also with those obtained in a jacketed equilibrium cell. Furthermore, the distribution ratio of caprolactam between toluene and water has been measured several times for the same initial caprolactam mass fraction in order to evaluate the repeatability. The obtained results are in very good agreement with the literature values for the acetone system and with those measured in the glass cell for the caprolactam systems, while a coefficient of variation of 1.8% for a seven times repeated measurement was found.

Introduction

The use of jacketed glass cells operated manually is the most commonly applied procedure for liquid−liquid equilibrium measurements. This approach is widely recognized as the standard procedure, and the majority of equilibrium data are obtained in this way.[1,2] However, this procedure involves laborious work in preparation of solutions, introduction of chemicals in the cell, sampling, sample preparation for chemical analysis, cleaning, and so forth. As a consequence, the number of experiments that can be performed per day is limited by the amount of work that can be performed by the experimenter. Furthermore, each of the steps done manually is subject to a potential experimenter's error that may reduce the accuracy of the results. Therefore, partial or, even better, full automation of the liquid−liquid equilibrium determination procedure would open the possibility for more measurements to be done per day, with a human- and time-independent accuracy. As a result, a more detailed experimental characterization of two-phase systems as well as more rapid screening of extraction solvents would be possible.

A short literature overview of the equipment used for this purpose, going from partial toward more complete automation and from automation of the extraction procedure in general toward specific automation of liquid−liquid equilibrium measurements, is given below.

Automated liquid handling systems are the most simple and common cases of automation. These systems are used by many laboratories dealing with small-scale batch liquid−liquid extraction in order to speed up the procedure. As examples, the programmable liquid handling workstations Quadra (Tomtec, USA)[3] and MicroLab AT Plus 2 (Hamilton, USA)[4] are mentioned. They are used for the rapid screening of extraction solvents needed for purification of combinatorial chemistry samples during drug development,[5] in quantification of drugs in biological fluids based on liquid−liquid extraction,[6] or for determination of components in human plasma, again based on liquid−liquid extraction.[7] Although such instruments significantly decrease a part of the manual handling by performing all liquid transfers, still, other operations involved in liquid−liquid extraction, like agitation, transfer of vessels, or sample analysis, have to be done either manually[6] or in other automated setups.

Mettler Toledo's automated liquid−liquid extraction unit Allex (Mettler Toledo Bohdan, USA) is an example of an instrument that could provide a higher level of automation. It can bring two liquids in contact, mix them, automatically determine the phase boundary after settling, and perform an efficient phase separation.[8−10] Nevertheless, the preparation of liquid solutions, the workup of samples for analysis, and the analysis itself still ask for manual work.

Full automation of liquid−liquid equilibrium measurements may be possible by using a system such as Zymate (Zymark, USA). Zymate is an advanced robotic system that consists of a centrally positioned robot arm and of modules located around it.[11] The arm moves vials from one module to another where an operation, such as liquid transfer, dilution, mixing, centrifugation, or analysis, is performed. Each module is a separate automated workstation and as such is locked into a position on a circular holder. All modules and the robot arm are controlled from the central system controller. Modules are chosen depending on the operations that need to be performed. Although such a robotic system would be able to handle all operations of a liquid−liquid equilibrium experiment, to our knowledge it is still not used for this purpose. The probable reasons are its rather high complexity, laboratory space requirements, and above all its high price that is at least 10 to 15 times higher than the price of a typical gas chromatograph unit, for example.

In contrast to the instruments mentioned up till now, which are aimed as wide application range systems, Meab's

* To whom correspondence should be addressed. Phone: +31-53-4895447. Fax: +31-53-4894821. E-mail: b.kuzmanovic@utwente.nl.

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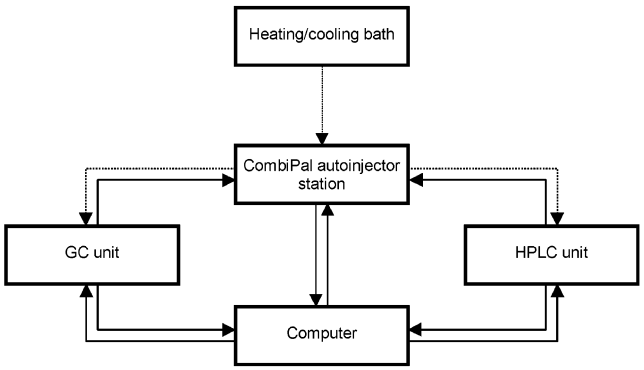

Figure 1. Sections of the workstation (dashed lines denote fluid flow, while full lines denote electrical signal flows).

Akufve (Meab, Sweden) is a setup developed specifically for measurement of the partitioning coefficients in liquid−liquid systems.[12] Akufve has not a robot arm for liquid transfer but a system of tubes and valves. Liquids introduced in this system are vigorously mixed and then drained through a valve−tube system into a continuous flow centrifuge for phase separation. Each of the phases is pumped back into the mixer and on its way can be sampled or connected to an on-line analysis unit. Although this unit provides a powerful tool for liquid−liquid equilibrium measurements with a significant level of automation, still, the sampling and preparation of samples in the case when no on-line analysis unit exists, as well as the preparation of solutions and their introduction in the system, have to be done manually.

A liquid−liquid flow extraction procedure, like the one applied to the determination of equilibrium partition coefficients of different compounds in the octanol−water system,[13] gives another possibility for automation of the liquid−liquid equilibrium measurements. The aqueous and organic phases are alternatively pumped into a capillary tube directly from the storage vials. Once in the capillary, the two-phase plug, led and followed by an air portion, is pumped back and forward through the tube until equilibrium is reached. The composition of both phases is analyzed by an analytical method that does not require sampling, like UV−vis spectrophotometry, when the plug passes through a detector. After data are acquired, the liquids are pumped out of the capillary and the next measurement can be done. This procedure provides a very high degree of automation using extremely low volumes of chemicals per experiment (in nanoliters). However, its limitation to nonsampling analytical methods only may be a significant disadvantage. If such a method is not applicable, as is often the case (especially for multicomponent systems), sampling of phases and sample preparation would have to be done and that could be very demanding.

In this paper, a setup for liquid−liquid equilibrium measurements that is fully automated, requires rather low equipment investments (comparable to the price of a typical gas chromatograph), and is very space efficient is presented. All operations, from preparation of aqueous and organic solutions, liquid transfer into a vial, agitation, phase sampling, sample preparation for analysis, and chemical analysis itself are done automatically. To show its applicability and explore the accuracy and repeatability of the procedure, the distribution ratio of acetone between toluene and water and the distribution ratio of caprolactam between an organic phase (toluene or benzene) and water have been measured. The results are compared with those reported in the literature and those obtained using a jacketed glass cell operated manually.

Workstation for Automated Measurements

The workstation is built from commercially available modules, which were only slightly adjusted in order to be used for the purpose of liquid−liquid equilibrium measurements. It includes a CombiPal advanced autoinjector station (CTC Analytics, Switzerland),[14] a gas chromatograph (GC) CP-3800 (Varian, USA), a high-pressure liquid chromatograph (HPLC) ProStar (Varian), a heating/cooling bath with external temperature control (Julabo Labortechnik, Germany), and a personal computer (see Figure 1).

The heart of the system is the CombiPal autoinjector station. It has three crossrails, *x*, *y*, and *z* (A1, A2, and A3 in Figures 2 and 3) which allow robot arm movement in all three dimensions. Besides allowing movement of the robot arm in the *x* direction, the *x*-crossrail (A1) also serves as the carrier on which different modules are mounted. Modules present in the configuration described in this

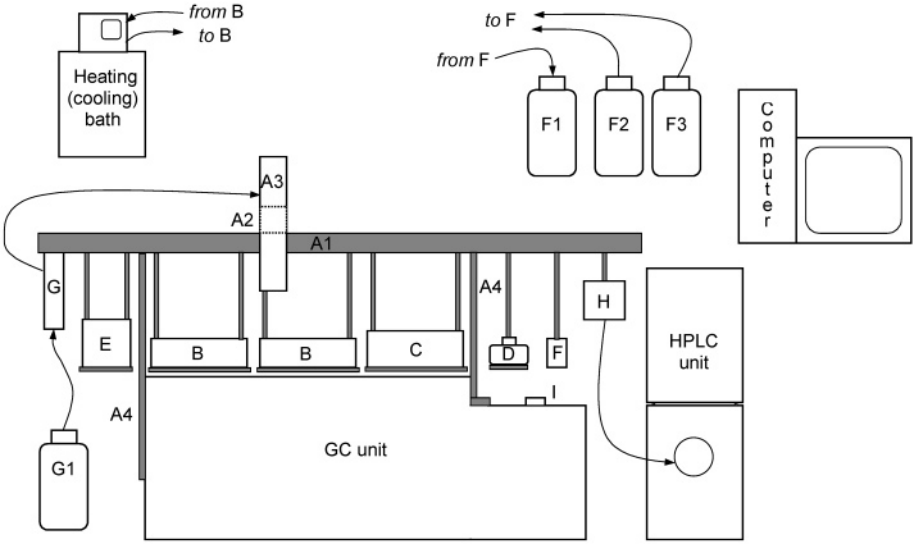

Figure 2. Scheme of the automated workstation: A1, *x*-crossrail; A2, *y*-crossrail (can be seen in Figure 3); A3, *z*-crossrail; A4, vertical holders; B, 2 mL vial tray holder with tray; C, 20 mL vial tray holder with tray; D, 100 mL vial holder with three vials; E, orbital shaker; F, washing station; F1, waste disposal tank; F2 and F3, washing solvent storage tanks; G, dilutor syringe; G1, diluting fluid storage bottle; H, remote HPLC injector; I, GC injector.

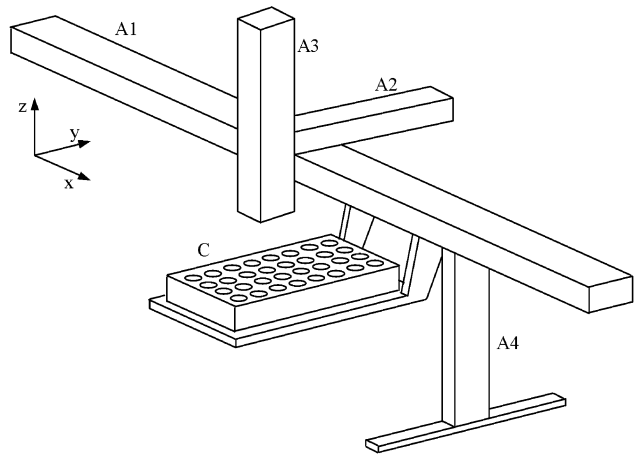

Figure 3. 3D scheme of the workstation's crossrails A1, A2, and A3 (one of the fixation holders A4 and the vial tray holder with tray C are included).

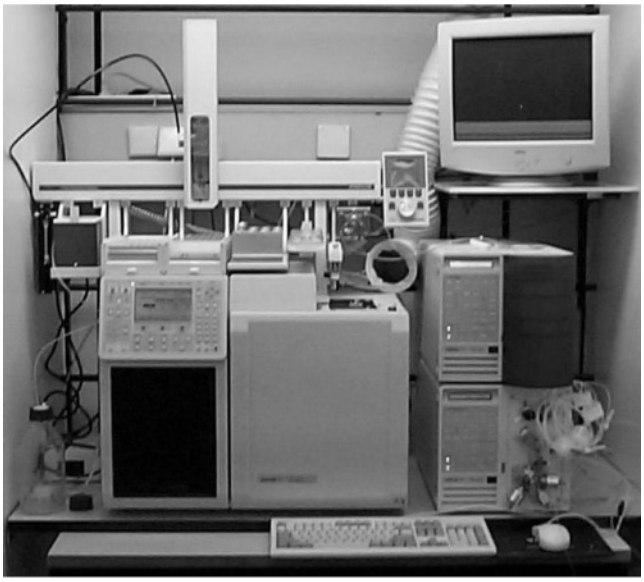

Figure 4. Photo of the workstation (the heating/cooling bath and computer are not shown).

paper and shown in Figures 2 and 4 are two 2 mL vial tray holders with trays (B), a 20 mL vial tray holder with tray (C), a 100 mL vial holder (D), an orbital shaker (E), a washing station (F), a dilutor syringe (G), and a remote HPLC injector (H). Furthermore, on the *x*-crossrail two vertical holders (A4) are present, with the help of which the CombiPal is attached on the gas chromatograph. The *z*-crossrail (A3) is the host for a syringe holder and the vial lifter. In this way, the syringe and vials can reach any coordinate within the range of the crossrails, that is, all modules on the crossrail as well as the GC injector (I). In the configuration discussed in this paper, an 80 μL syringe is mounted on the syringe holder.

The syringe's plunger can be moved in the *z* direction independently on the movement of the syringe, allowing injection or ejection of the liquid. Very accurate control of the plunger's position in combination with calibration of its initial position before any injection allows very repetitive liquid transfers. The repeatability, characterized by the relative standard deviation of a 10 times repeated transfer of 20 μL of water by this syringe, that is, at 25% of its full capacity, is measured to be 0.5%. It should be emphasized that the plunger can be moved only in increments of 0.1 mm. This means that the transferred amount would differ from the required amount by not more than 0.1% if quantities in the full range of the syringe are transferred (full scale has a length of 48.0 mm). However, the error increases up to 1% when only 10% of its capacity is used. Therefore, transferring quantities in the lower part of the syringe's capacity range should be avoided.

By use of this automated workstation, the liquid−liquid equilibrium is established in 2 mL glass vials closed by a metal crimp seal with a septum. Seals made of metal enable picking-up and moving of a vial by the magnetized end of the vial lifter. The septum has a Teflon/Silicone/Teflon layer structure providing satisfying chemical stability toward many solvents.

Before the automated procedure can be initiated, certain preparative activities have to be done by the experimenter. The CombiPal operation sequence has to be defined (it needs to be defined only once and can be reused as many times as required), the storage tanks have to be filled with the chemicals required for the experiments, the empty sealed vials, in which equilibrium will be established, have to be placed in their positions, and finally, the sample sequence list for gas and/or liquid chromatography has to be defined.

The first step of the automated procedure is the transfer of liquids by syringe from the storage vials into the empty, sealed equilibrium vials that are placed in trays (Figure 2, B). The 20 mL vials (in tray C), 100 mL vials (D), and 1 L bottle (G1) are used for storage of chemicals required for the experiments. It should be emphasized that since this system is able to handle liquids only, solid chemicals have to be provided in solution. Up to thirty-two 20 mL and three 100 mL vials and one 1 L bottle can be used in the configuration described in this paper. Chemicals from the 20 and 100 mL vials are transferred directly by the 80 μL syringe, while for distribution of liquid from the 1 L vessel the 2.5 mL dilutor syringe (G) connected by plastic tubes to the 80 μL syringe is used. The tube originates in the bottle, goes via the dilutor syringe, and ends in the sideport of the 80 μL syringe. The dilutor syringe sucks the required quantity of the liquid from the bottle and moves it through the sideport of the 80 μL syringe into a vial on the tray (B). For this purpose, the plunger of the 80 μL syringe is positioned above the sideport opening so that the liquid can pass through this syringe into a vial.

Once this is done, the vials are lifted and moved by robot arm into the orbital shaker (E) for agitation. Since the shaker can accommodate not more than six vials per run, the agitation has to be done in groups of six, if only one shaker is installed like in our configuration. The direction of the shaker's orbital movement is alternated, with a pause between changes, where the rotation intervals and the duration of the break can be specified. Electrical heaters in the shaker allow a regulation of the temperature during agitation in the range from room temperature up to (300 ± 0.5) °C.

After agitation (the duration required for agitation has to be determined in advance), the vials are picked up and moved back into their original positions in a tray, where phase settling occurs. Heating/cooling fluid flows through the inner space of this tray and maintains the desired temperature during settling. Each 2 mL tray is made from metal and has two openings at the backside for connection of the tubes coming from the heating/cooling bath. In the current configuration, both trays are connected to the same bath. For the purpose of temperature regulation, a small PT-100 probe (uncertainty of 0.01 °C at 25 °C), connected to the heating/cooling bath, is submerged in a 2 mL vial

filled with water and this vial is placed in one of the trays. Thereby, the temperature of the circulating fluid can be adjusted to maintain the required temperature of the liquid in the vials. In this way, the temperature of liquid in one single position in one of the trays represents the temperature for all positions and both trays. Knowing that the maximum temperature difference between any two different positions in a tray is measured to be not more than 0.1 °C, this approach is justified.

After the settling is completed (the duration required for settling has to be determined in advance), samples of both phases are taken. This is done by the syringe from the top of the vials, first a sample of the upper phase and then a sample of the lower phase. For this operation, a low needle penetration and retraction speed (800 μm/s) and liquid suction rate (1.5 μL/s) are applied to maintain the system as undisturbed as possible. The penetration (retraction) speed can be chosen in the range of 1 μm/s up to 10 mm/s, while the suction rate ranges from 1.0 μL/s up to 0.5 mL/s. To minimize contamination of the lower phase sample due to the needle travelling through the upper phase, a defined amount of the withdrawn sample was first ejected into the waste (to wash the needle with the sample) before the sample was disposed into a vial. The same is done with the last portion present in the syringe. Additionally, the sample of the lower phase was taken close to the bottom of the vial allowing needle wetting by the lower liquid before suction is commenced. Each sample is transferred into an empty, sealed 2 mL vial and is diluted in an adequate solvent. The dilution is done to enable sample analysis, but also to prevent possible second phase formation due to a possible temperature change. The dilution solvent is stored in the 1 L bottle (Figure 2, G1), and it is therefore dispensed in the sample vial using the dilutor syringe (G). Finally, if required for quantitative analysis, an internal standard can also be introduced, either from a separate storage vial or together with the dilution solvent. After this is done, the sample vials are transferred into the orbital shaker and agitated for several minutes to homogenize the solution. Finally, these prepared samples are injected either into the gas chromatograph injector (I) or into the external injection valve of the high-pressure liquid chromatograph (H) for quantitative analysis. With calibration curves determined and implemented in the analysis software, the component concentrations in both phases will be directly obtained.

It should be emphasized that before any liquid transfer, the syringe and its needle are washed in the washing station (F). The station has two ports for washing and one for waste disposal. Washing ports are connected to the washing solvent 1 L storage tanks (F2, F3), and waste disposal to a waste tank (F1). Any liquid waste generated during the experiment is disposed in this port.

The system is operated from the personal computer connected to the CombiPal, gas chromatograph, and high-pressure liquid chromatograph as shown in Figure 1. Windows-based custom-made software Cycle Composer (CTC Analytics) is used to operate the CombiPal autoinjector. For the operation of the chromatographs and chromatogram analysis, Star software (Varian) is used.

Liquid−Liquid Equilibrium Measurements

By use of the automated workstation, liquid−liquid equilibria were measured for three two-phase systems often found in the literature: toluene + water + acetone, toluene + water + caprolactam, and benzene + water + caprolactam. The reason for choosing the toluene−water−acetone system is that it has been declared as one of the standard test systems for liquid−liquid extraction by the Society for Chemical Engineering and Biotechnology (DECHEMA)[15] and is therefore very well characterized in the literature. The other two systems, although not recognized as standard test systems, are selected because their characterization is part of our wider research activities and they also represent cases with significantly different physical properties (interfacial tension, viscosity, etc.) than the acetone system. The equilibrium is measured in the first case at 20 °C and for the last two systems at 40 °C (toluene) and at 20 °C (benzene). The equilibrium data determined for the acetone system at the automated workstation are compared with the values reported in the literature that are recognized as the reference for this system.[16] On the other hand, since no recognized reference exists for the caprolactam systems, the equilibrium composition for these cases is measured in a jacketed glass cell operated manually and those results, together with the values found in the literature,[17−20] were used for comparison.

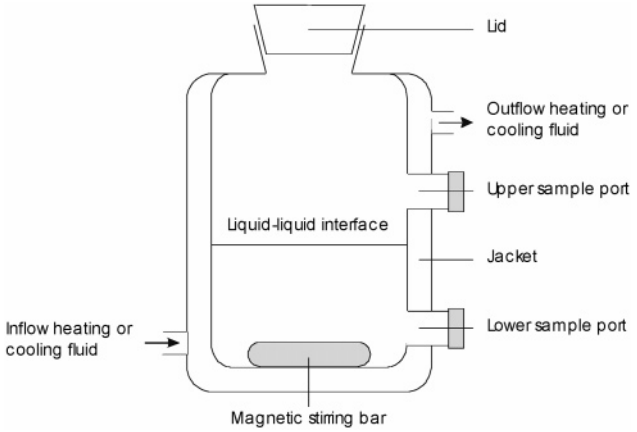

Figure 5. Manually operated glass cell used for the determination of liquid−liquid equilibria.

Chemicals. Toluene (purity, 99%) was supplied by Fluka (USA), benzene (purity, >99.5%) by Riedel de Haën (USA), ϵ-caprolactam (purity, 99%) by Sigma-Aldrich (USA), ethanol (purity, 99.8%), acetone and methanol (purity, >99.8%) by Merck (Germany), and 1-methyl-2-pyrrolidone (purity, 99%) by Acros (Belgium). All chemicals were used as received. MilliQ water was used in all experiments.

Equilibrium Measurements in the Jacketed Glass Cell Operated Manually. A scheme of the jacketed glass cell is shown in Figure 5. The cell has an inner chamber of about 55 mL that is surrounded by a jacket for temperature control. The jacket is connected to a Julabo F12 heating/cooling bath (Julabo Labortechnik, Germany), and water was used as the heating/cooling fluid. The inner chamber has two sampling ports, one in the upper half and the other in the lower half of the cell, allowing sampling of both phases. The cell stands on the plate of a multiple point magnetic stirrer (Variomag), and a magnetic bar (30 mm length) is used for agitation.

Equilibrium measurements were performed as follows. Twenty milliliters of the organic solvent (toluene or benzene) and 20 mL of an aqueous caprolactam solution were introduced in the vessel by a pipet. The caprolactam mass fraction in the initial aqueous solution was in the range from 0 up to 60 mass %. After introduction of the solutions, the mixture was stirred at 450 rpm at a regime of 90 s stirring and 20 s pause. After equilibrium was reached (the time of agitation required to reach equilibrium was determined prior to equilibrium experiments), the mixture was

left to settle for 1 h. During the agitation and settling, the temperature of the fluid in the vessels was kept constant at the required value with an uncertainty of 0.1 °C. After the phases settled, samples from both the organic (100 μL) and the aqueous layer (20 μL) were taken with a syringe.

Equilibrium Experiments on the Automated Workstation. On the automated workstation, the equilibrium was established in 2 mL glass vials in which acetone or 60 mass % aqueous caprolactam solution, pure water, and organic solvent (toluene or benzene) were introduced. In the case of caprolactam as the solute, the volume of organic solvent was 900 μL, the volume of caprolactam solution was in the range of 54 μL to 900 μL, and the volume of pure water depended on the amount of caprolactam solution and was added in such quantities that the sum of caprolactam solution and pure water volume is 900 μL. In this way, the initial organic to aqueous phase volume ratio was equal to 1, while the mass fraction of caprolactam in the aqueous phase was varied. In case of acetone, equal volumes of toluene and pure water were introduced, in such way that the total liquid volume was 1800 μL. The organic solvent and pure water were stored in 100 mL vials, while a 20 mL vial was used for acetone or the 60 mass % caprolactam solution.

It should be emphasized that before any liquid transfer, the syringe was first washed in ethanol and then in toluene/benzene, water, or acetone. The washing station and a 20 mL vial filled with toluene or benzene, a 20 mL vial filled with water, and one filled with acetone were used for this purpose.

After the filling, the vials were transferred into the orbital shaker and agitated. The shaking was done by applying 750 rpm, with 30 s of rotation in one direction, a 5 s pause, and 30 s of rotation in the opposite direction. The time of shaking required to reach equilibrium was determined on the same automated workstation prior to equilibrium experiments (see Equilibration Time in Results and Discussion). The temperature inside the shaker was kept either at 20 °C or at 40 °C. Here, it has to be emphasized that the shaker is capable of heating only (no cooling is currently available). Therefore, the setup is limited to experiments at temperatures higher than the room temperature. When these experiments were done, the room temperature was below 20 °C. After shaking, the vials were returned to the trays for settling. The temperature in the 2 mL trays was also maintained at 20 °C or at 40 °C, depending on the experiment. Water was used as the heating/cooling fluid. The settling was done for at least 1 h.

After settling, 100 μL of the organic phase and 25 μL of the aqueous phase were sampled in the caprolactam case, while 180 μL of each phase was taken in the acetone case. Each sample was transferred into an empty 2 mL vial. Caprolactam samples were diluted with 1000 μL of ethanol, and after that 50 μL of the internal standard was added. Acetone samples were diluted with 400 μL of methanol, and 65 μL of internal standard was introduced. The vials were transferred into the shaker, agitated for 3 min, and returned back into the 2 mL trays to settle for at least 10 min to achieve a homogeneous solution. After that, a sample was injected into the gas chromatograph for quantitative analysis.

Chemical Analysis. The mass fraction of caprolactam in both the organic and the aqueous phase was determined in a gas chromatograph, CP-3800 (Varian), equipped with a EC-WAX column (30 m, 0.32 mm; 0.25 μm film thickness) and a FID detector. During the analysis, the column temperature was raised from 60 °C to 70 °C with an increment of 10 °C/min and then from 70 °C to 250 °C with an increment of 50 °C/min. The temperatures of the injector and detector were kept constant at 225 °C and 250 °C, respectively, with a pressure in the injector of 275 kPa (analysis of samples from jacketed glass vessel) or of 138 kPa for analysis of samples from the automated workstation. The split ratio of 10 was used in both cases. For the analysis performed at the automated workstation, hydrogen was used as the carrier gas with an initial flow of 1.5 mL/min, while a sample of 1.5 μL was injected into the column. In the case of glass cell experiments, helium was used as the carrier gas with an initial flow of 14.2 mL/min and a sample of 0.3 μL was injected into the column. Quantification of caprolactam in the sample was done by using an internal standard method where 1-methyl-2-pyrrolidine was used as the internal standard.

A 10 mass % aqueous caprolactam solution was prepared and analyzed four times to test the repeatability and the accuracy of the GC analysis. The mean value of 9.79 mass % is found with uncertainty of 0.26 mass % (determined as standard deviation).

The mass fraction of acetone in both the organic and the aqueous phase was determined by the same gas chromatograph, but equipped with a CP-SIL 5CB column (25 m, 0.15 mm; 1.2 μm film thickness). In this case, the column temperature was raised from 60 °C to 100 °C with an increment of 10 °C/min and then from 100 °C to 270 °C with an increment of 60 °C/min. The temperatures of the injector and detector were kept constant at 270 °C and 300 °C, respectively, with a pressure in the injector of 173 kPa and a split ratio of 40. Hydrogen was used as the carrier gas with an initial flow of 0.9 mL/min. Quantification of acetone in the sample was also done by using 1-methyl-2-pyrrolidone as the internal standard.

Data Analysis. The distribution ratio of a solute i $(K_D)_i$ is defined as the ratio of the determined solute mass fraction in the organic phase (w_i^{org}) to the one in the aqueous phase (w_i^{aq}) at equilibrium:

$$(K_D)_i = \frac{w_i^{org}}{w_i^{aq}} \quad (1)$$

This distribution ratio was used for presentation of the experimental results and their comparison with the literature values.

Results and Discussion

Equilibration Time. Prior to equilibrium measurements, the time of agitation required to reach equilibrium for specific experimental conditions (experimental setup, components, temperature) was determined. Although the time to reach equilibrium may somewhat differ for different initial mass fractions of the solute due to a change of physical properties of the system (like viscosity, interfacial tension, and density), this difference was not considered significant. Therefore, the mass fraction change of acetone or caprolactam in the organic or aqueous phase was monitored as a function of time of agitation for one initial solute mass fraction. For the acetone case, the results obtained on the automated workstation are given in Figure 6, while for caprolactam those obtained in the jacketed glass cell are given in Figure 7 and those on the automated workstation in Figure 8.

In the jacketed glass cell, it seems that after 25 min of agitation the equilibrium for the caprolactam extraction was reached. On the automated workstation, a significantly

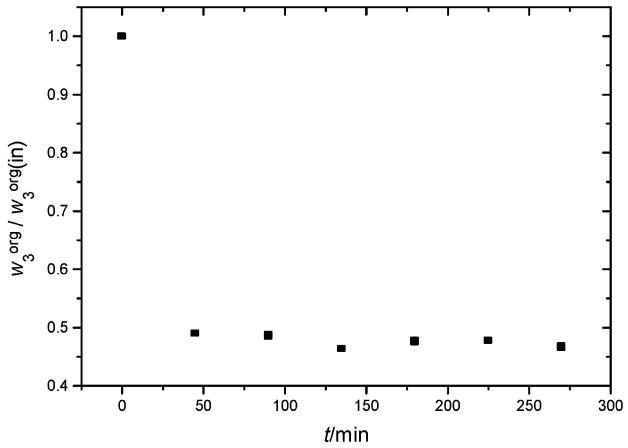

Figure 6. Profile of the normalized mass fraction of acetone in the organic phase as a function of time of agitation *t* in the system toluene (1) + water (2) + acetone (3) at 20 °C. Introduced quantities: 900 μL of toluene, 225 μL of acetone, and 675 μL of water.

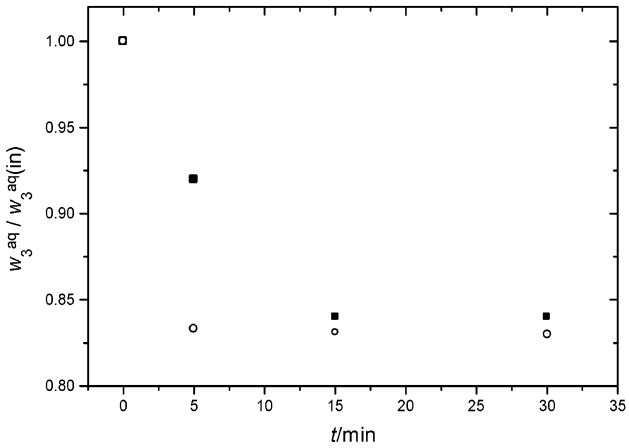

Figure 7. Profile of the normalized mass fraction of caprolactam in the aqueous phase as a function of time of agitation *t* obtained in the jacketed glass cell: ■, benzene (1) + water (2) + caprolactam (3) at 20 °C; ○, toluene (1) + water (2) + caprolactam (3) at 40 °C. Introduced quantities: 20 mL of toluene or benzene and 20 mL of 10 mass % aqueous caprolactam solution.

longer time was required for both the caprolactam and the acetone system. In the first case, it was in the range of 250 min for both solvents, while around 130 min was enough for acetone extraction. Obviously, the agitation of liquids in the 2 mL round vials by the orbital shaker is far less efficient than agitation in the large jacketed glass cell by a magnetic stirrer. Furthermore, it is clear that physical properties of the system also influence equilibration time. With the same energy input, the more viscous caprolactam solution needs twice the time to reach equilibrium than is the case for the acetone system.

Equilibrium Results. The distribution ratios of acetone and caprolactam have been measured as a function of the solute equilibrium mass fraction in the aqueous phase. The results are shown in Figures 9−11 (for the values see Tables 1 and 2). The accuracy of the measurements performed on the automated workstation has been characterized by the deviation of measured results from the values measured in the jacketed glass cell, but also from those found in the literature.

The measured values of the distribution ratio of acetone are all exactly within the cloud of the literature data, with the exception of the point at 25 mass % acetone in the aqueous phase, which is at its border. Similar results are

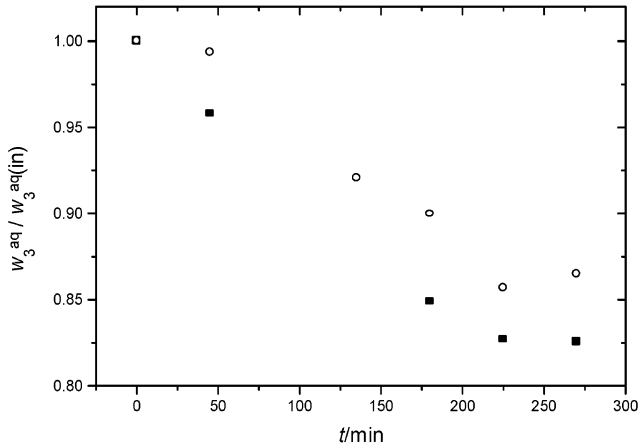

Figure 8. Profile of the normalized mass fraction of caprolactam in the aqueous phase as a function of time of agitation *t* obtained at the automated workstation: ■, benzene (1) + water (2) + caprolactam (3) at 20 °C; ○, toluene (1) + water (2) + caprolactam (3) at 40 °C. Introduced quantities: 900 μL of benzene or toluene, 225 μL of 60 mass % aqueous caprolactam solution, and 675 μL of water.

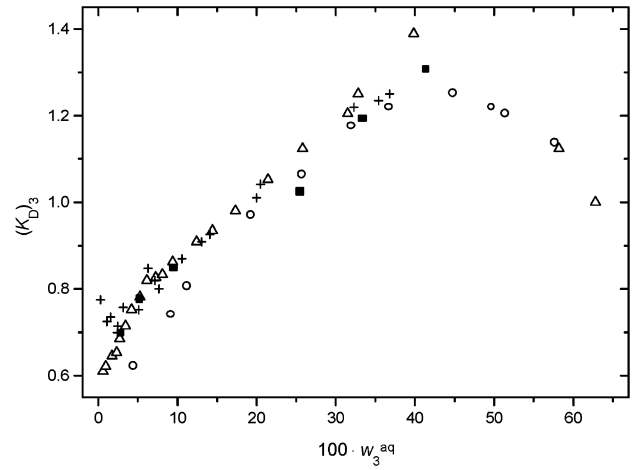

Figure 9. Distribution ratio of acetone in the system toluene (1) + water (2) + acetone (3) at 20 °C as a function of the mass fraction of acetone in the aqueous phase at equilibrium: ■, automated workstation, this work; △, Hackl et al., 1975 (ref 16); ○, Pavasovic, 1975 (ref 16); +, Brandt et al., 1975 (ref 16).

obtained for the systems toluene−water−caprolactam and benzene−water−caprolactam, where the values measured on the automated workstation generally lay in the cloud of data acquired in the jacketed glass cell. Furthermore, the literature values for the last two systems also agree with the findings presented in this work, with the exception of the data reported by Morachevskii et al.[18] for the benzene−water−caprolactam system, for the lower mass fraction range of caprolactam. From obtained results for all three systems, it may be concluded that a very good accuracy of the automated workstation exists.

The repeatability of the measurements conducted on the automated workstation has been evaluated by determining the equilibrium distribution ratio of caprolactam in the toluene−water−caprolactam system seven times for the same initial caprolactam mass fraction in the aqueous phase. The results are shown in Table 3.

The coefficient of variation of the seven measurements presented in Table 3 is 1.8%, which may be considered as very good repeatability. However, if statistical error analysis would be performed on those data, it would be found that measurement 4 exceeds the 2 times standard deviation

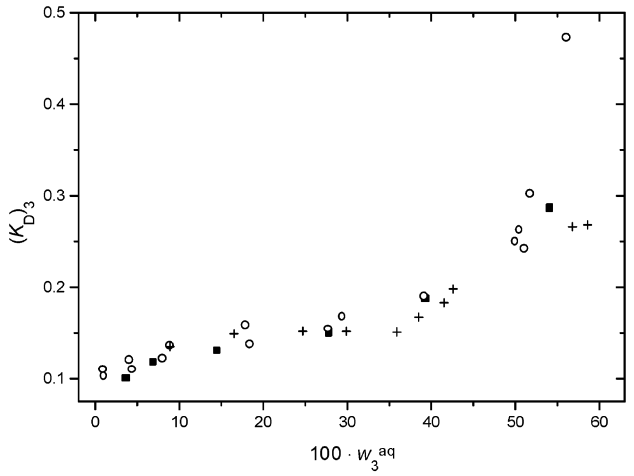

Figure 10. Distribution ratio of caprolactam in the system toluene (1) + water (2) + caprolactam (3) at 40 °C as a function of the mass fraction of caprolactam in the aqueous phase at equilibrium: ■, automated workstation, this work; ○, jacketed glass cell, this work; +, Pajak et al., 1991 (ref 17).

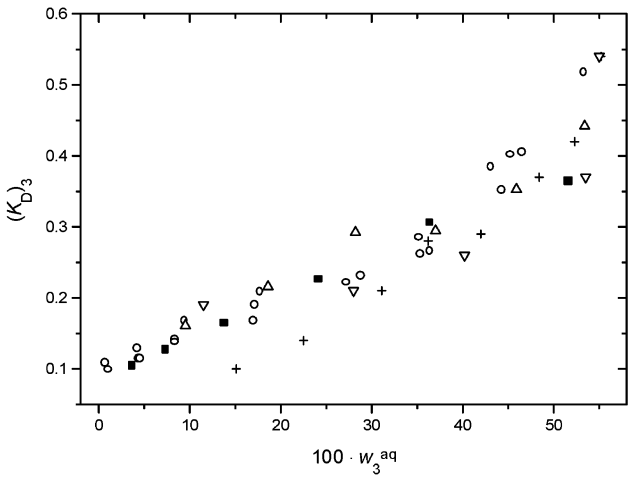

Figure 11. Distribution ratio of caprolactam in the system benzene (1) + water (2) + caprolactam (3) at 20 °C as a function of the mass fraction of caprolactam in the aqueous phase at equilibrium: ■, automated workstation, this work; ○, jacketed glass cell, this work; +, Morachevskii et al., 1960 (ref 18); ▽, Tettamanti et al., 1960 (ref 19); △, de Haan and Niemann, 2001 (ref 20).

Table 1. Distribution Ratios Determined at the Automated Workstation

$100w_3^{aq}$	$(K_D)_3$	$100w_3^{aq}$	$(K_D)_3$	$100w_3^{aq}$	$(K_D)_3$
		Acetone System[a]			
2.94	0.697	9.58	0.848	33.4	1.19
5.23	0.777	25.6	1.02	41.5	1.31
		Caprolactam−Toluene System[b]			
3.69	0.100	14.6	0.130	39.4	0.187
6.97	0.117	27.9	0.150	54.1	0.286
		Caprolactam−Benzene System[c]			
3.63	0.104	13.8	0.164	36.4	0.306
7.37	0.127	24.2	0.226	51.7	0.364

[a] Toluene (1) + water (2) + acetone (3) at 20 °C. [b] Toluene (1) + water (2) + caprolactam (3) at 40 °C. [c] Benzene (1) + water (2) + caprolactam (3) at 20 °C.

range and hence may be characterized as a bad data point. Therefore, although the repeatability of the automated workstation may be characterized as good, one should be aware that bad data points might occur.

Table 2. Distribution Ratios Determined in the Jacketed Glass Cell

$100w_3^{aq}$	$(K_D)_3$	$100w_3^{aq}$	$(K_D)_3$	$100w_3^{aq}$	$(K_D)_3$
		Toluene System[a]			
0.92	0.110	17.9	0.158	50.5	0.262
1.05	0.103	18.4	0.138	51.0	0.242
4.02	0.120	27.8	0.154	51.8	0.302
4.46	0.110	29.4	0.167	56.1	0.473
8.06	0.122	39.2	0.189	56.5	0.464
8.89	0.136	50.0	0.250		
		Benzene System[b]			
0.71	0.109	9.43	0.168	36.4	0.265
0.72	0.109	17.0	0.167	43.1	0.384
1.04	0.100	17.2	0.190	44.4	0.352
4.26	0.129	17.7	0.209	45.2	0.402
4.47	0.114	27.2	0.222	46.5	0.405
4.62	0.115	28.8	0.231	53.3	0.518
8.33	0.141	35.2	0.285	54.4	0.519
8.36	0.138	35.4	0.262		

[a] Toluene (1) + water (2) + caprolactam (3) at 40 °C. [b] Benzene (1) + water (2) + caprolactam (3) at 20 °C.

Table 3. Repeatability of an Equilibrium Measurement Conducted on the Automated Workstation for the Toluene (1) + Water (2) + Caprolactam (3) System at 40 °C[a]

measurement	$100w_3^{org}$	$100w_3^{aq}$	$10(K_D)_3$
1	1.86	14.2	1.31
2	1.90	14.5	1.31
3	1.89	14.2	1.33
4	1.92	14.0	1.37
5	1.86	14.3	1.30
6	1.85	14.1	1.31
7	1.90	14.5	1.31
average	1.88 ± 0.03	14.3 ± 0.2	1.32 ± 0.02

[a] The initial mass fraction of caprolactam in the aqueous phase w_3^{aq} (in) was 15.6%.

Conclusions

The workstation described in this paper is a promising option for full automation of liquid−liquid equilibrium measurements. It performs all operations involved in these measurements, from initial solution preparation, through equilibrium establishment and sampling, to solute concentration analysis in both phases, with no need for any human assistance at all. Chemical analysis by gas or high-pressure liquid chromatography used on this workstation is also fully automated. Although these analytical techniques are rather demanding and require sample treatment before analysis itself, they are very often the best options, especially for multicomponent mixtures. In the configuration described in this paper, up to 65 equilibria can be measured continuously with no necessity for human interference. This is based on the need for one 2 mL vial for equilibrium establishment and two vials for each phase sample, and the presence of two 2 mL vial trays in the configuration. Up to 36 equilibrium experiments per day, compared to only 3 that could be done in a glass cell, in the case of the organic solvent−water−caprolactam system, can be accomplished using this workstation.

On the basis of the equilibrium measurements in the three test systems, toluene−water−acetone, toluene−water−caprolactam, and benzene−water−caprolactam, it is concluded that the measurements on the automated workstation are done with good accuracy, but also that they are easily repeatable.

By establishing equilibrium in 2 mL vials, as done here, not more than 4 mL of liquid waste per experiment

(considering sample dilution as well) is produced. This amount is significantly lower than that generated in a jacketed glass cell experiment, which typically ranges from 30 mL up to 200 mL.

Although larger capital investments than in the case of a jacketed glass cell must be provided, the significant decrease in the experimenter costs justifies such an investment. On the other hand, compared to the price of other systems with the same level of automation, this workstation is significantly cheaper. Furthermore, its compact size and possibility to be mounted on the top of a gas chromatograph do not ask for significant space. In the case described in this paper, the whole workstation is operated in a laboratory room of 1.45 m by 1.32 m and 2.50 m in height.

However, certain limitations and issues to be improved are present:

(1) One of the limitations is that the system behavior must be known before experiments are performed on the workstation. For example, the position of the phase boundary at equilibrium, the amount of each phase required for sampling, or the degree of dilution must be determined beforehand.

(2) In some cases, when handling viscous liquids for example, an air bubble may form inside the syringe. This bubble is located at the surface of the plunger tip and is never larger than several percent of the syringe capacity. To overcome this shortcoming, an excess of 5 μL of liquid is always sucked in the syringe, leaving the bubble inside the syringe after ejection. Furthermore, before performing experiments with such liquids, the rate of suction, the number of strokes, and the rate of ejection are optimized to eliminate or to minimize the size of the bubble.

(3) Further optimization can be done on the manner in which larger liquid volumes are transferred. Using an 80 μL syringe for transfer of amounts up to 1 mL requires several repetitive cycles and therefore more time. Introducing more 2.5 mL dilutor syringes, such as the one used in this configuration for dilution of samples, would improve this operation.

(4) The agitation in the 2 mL vials performed in the orbital shaker also needs optimization. A change of the vial shape, from a round into a square cross section, or introduction of a glass bead in the vial could improve the quality of mixing and accelerate the rate of equilibration.

(5) Furthermore, the temperature range of experiments could be broadened and not limited by the room temperature, if cooling during agitation is also enabled.

(6) Finally, putting more shakers on the crossrail would allow more parallel measurements.

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