Optical fiber-based on-line UV/Vis spectroscopic monitoring of chemical reaction kinetics under high pressure in a capillary microreactor†

Fernando Benito-Lopez,[a] Willem Verboom,*[a] Masaya Kakuta,[b] J. (Han) G. E. Gardeniers,*[b] Richard J. M. Egberink,[a] Edwin R. Oosterbroek,[b] Albert van den Berg[b] and David N. Reinhoudt[a]

Received (in Cambridge, UK) 12th January 2005, Accepted 8th April 2005
First published as an Advance Article on the web 22nd April 2005
DOI: 10.1039/b500429b

With a miniaturized (3 μL volume) fiber-optics based system for on-line measurement by UV/Vis spectroscopy, the reaction rate constants (at different pressures) and the activation volumes ($\Delta V^{\neq}$) were determinined for a nucleophilic aromatic substitution and an aza Diels–Alder reaction in a capillary microreactor.

Application of (high) pressure is a very important methodology to enhance the rate of a variety of organic reactions.[1] In general, reactions accompanied by a decrease in molar activation volume ($\Delta V^{\neq}$) are accelerated by pressure. The molar activation volume of a reaction (the difference in molar volume between the intermediate state and the reactants) provides valuable information on the mechanism of a (bio)chemical reaction and the molecular intermediates involved in it.

In general, high-pressure chemistry is regarded as a technique that requires specialized equipment with strict safety precautions. It is trivial that miniaturization of the reaction system will relax safety regulations, so that high pressure experimentation will become more readily available. Therefore, we decided to build a miniaturized microreactor platform for the study of the pressure dependence of (the rate of) organic reactions. The ultimate goal is to build a microsystem for parallel synthetic organic chemistry, based on the "Lab-on-a-chip" concept,[2] which has integrated components for on-line chemical analysis and reaction control, like thin film heaters or a miniaturized electrochemical pressure source, which has been demonstrated to achieve pressures over 1300 bar.[3]

As a first step towards such a system, we describe in this communication a miniaturized experimentation platform based on conventional HPLC tools coupled to a capillary microreactor. As a proof-of-concept a capillary-based system has been used to study the pressure dependence of organic reactions at pressures of up to 600 bar. Although this pressure range does not give the full advantage of high pressure chemistry, the range is wide enough to study the rate enhancement and to collect essential information to determine the molar activation volumes of reactions. To monitor the course of the reactions, a fiber-optic system for on-line UV spectroscopy is used.

† Electronic supplementary information (ESI) available: plots of the reaction of **1b** with **2a** under different pressures, Table with rate constants of the reaction of halonitrobenzenes **1** with amines **2**, and Table with rate constants and activation volumes of the reaction of **1a** with amines **2a,b**. See http://www.rsc.org/suppdata/cc/b5/b500429b/

*w.verboom@utwente.nl (Willem Verboom)
j.g.e.gardeniers@utwente.nl (J. (Han) G. E. Gardeniers)

A schematic representation of the microreactor set-up is given in Fig. 1. It consists of a fused silica capillary (volume of 3 μL) running through a stainless steel cross, a 6-port valve for sample inlet and outlet, and a HPLC pump as pressure generator. *Via* an optical fiber, connecting the silica capillary and an UV/vis spectrophotometer, the course of the reactions was followed. High pressure sources delivering pressures up to several hundreds of bars are generally available for HPLC, a rather common analytical method, which can be used without the exceptional safety regulations that normally apply in high-pressure chemistry labs. Although high-pressure fluidic connections and valves are still a problem in lab-on-a-chip systems,[4] for our applications we used the commercially available connectors which were tested up to 700 bar, and can be used in a capillary-based microreactor system without adjustment.

Some years ago Ibata *et al.*[5] reported that nucleophilic aromatic substitution reactions of electron-withdrawing group containing aromatic halides with various amines could be accelerated by pressure. This type of reaction proceeds *via* a Meisenheimer dipolar intermediate. The effect of pressure on this reaction is explained by the fact that both bond formation and charge separation occur in the transition state.

We selected this reaction to study it in more detail in our microreactor set-up. Therefore *p*-halonitrobenzenes (**1**) (X = F, Cl, Br) were reacted with a ten-fold excess of pyrrolidine (**2a**), piperidine (**2b**), and morpholine (**2c**) in THF at 1, 200, 400, and 600 bar to give the *p*-*N*,*N*-dialkylamino-nitrobenzenes (**3a–c**)

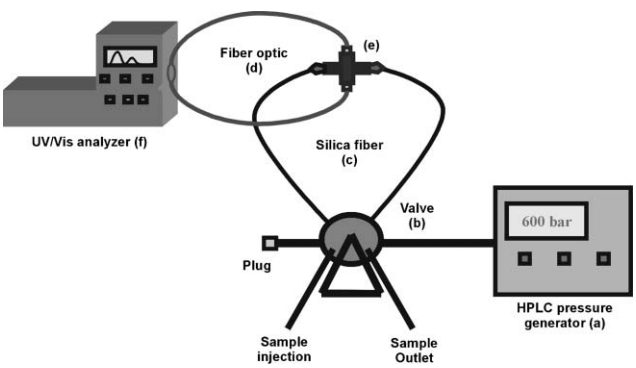
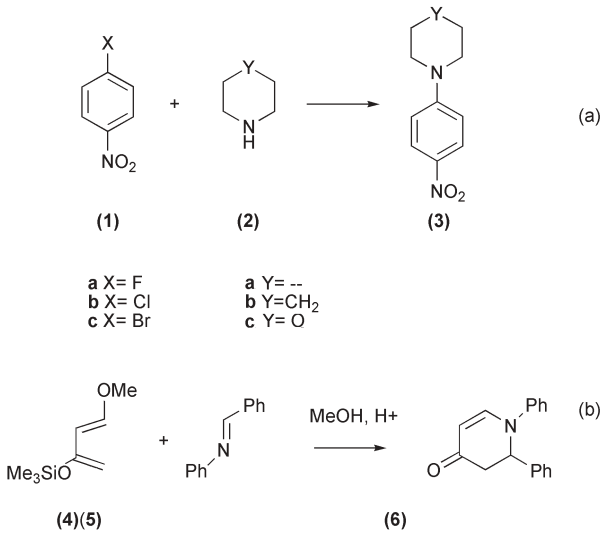


Fig. 1 Schematic representation of the high pressure UV capillary reactor system showing: high pressure generator (a), six-port valve for injection (b), capillary microreactor (c), optical fiber (d), UV/Vis light source (e), and UV/Vis detector (f).



Scheme 1 Aromatic nucleophilic substitution (a) and aza-Diels–Alder reaction (b).

(Scheme 1a). The product formation was monitored by the increase of the absorption peak at 391 nm in the UV/Vis spectra.

Rate constants k of the different reactions at the different pressures were calculated from the increase of the absorption at 391 nm using a pseudo first order kinetic equation (eqn. 1). The resulting rate constant k_{obs} has to be divided by the amine concentration to obtain the second-order rate constant k.

$$A_t = A_\infty[1 - \exp(-k_{obs}t)] \quad (1)$$

Where A_t is the absorbance at time t and A_∞ is that after infinite time. As an illustration, Fig. 2 shows the second order rate constants k of the reaction of 1-fluoro-4-nitrobenzene (**1a**) *vs.* pressure for the three different amines (**2**). The rate constants (k_{obs} and k) at 600 bar are summarized in Table 1.

The k values show the following reactivity order of the leaving groups: F > Cl > Br.[6] However, in the case of pyrrolidine (**2a**), 1-bromo-4-nitrobenzene (**1c**) reacts somewhat faster than the corresponding chloro derivative (**1b**) (6.60×10^{-4} M^{-1} s^{-1}, *vs.* 5.56×10^{-4} M^{-1} s^{-1} at 600 bar). A similar behavior has been

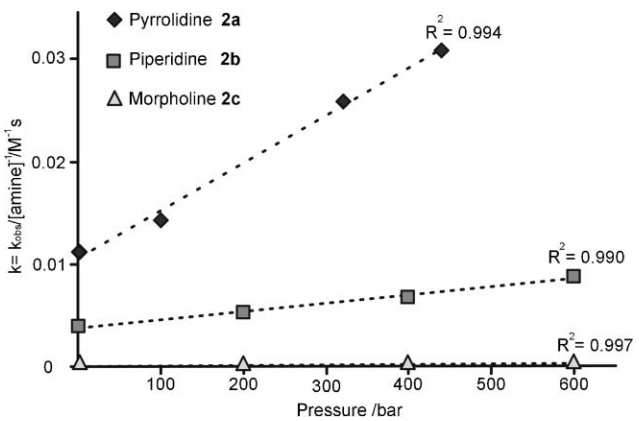


Fig. 2 Nucleophilic aromatic substitution reaction of 1-fluoro-4-nitrobenzene (**1a**) (0.125 M) with amines **2a–c** (1.25 M) in THF at four different pressures.

Table 1 Rate constants for the nucleophilic aromatic substitution reaction of halonitrobenzenes **1** with amines **2** at 600 bar

Halonitrobenzene[a]	Amine[a]	k_{obs}/s^{-1}	k/M^{-1} s^{-1}
1a	**2a**	3.86×10^{-2}	3.09×10^{-2}
1b	**2a**	6.95×10^{-4}	5.56×10^{-4}
1c	**2a**	8.25×10^{-4}	6.60×10^{-4}
1a	**2b**	1.10×10^{-2}	8.80×10^{-3}
1b	**2b**	3.62×10^{-4}	2.89×10^{-4}
1c	**2b**	3.22×10^{-5}	2.57×10^{-5}
1a	**2c**	9.87×10^{-5}	7.89×10^{-5}
1b	**2c**	6.76×10^{-5}	5.41×10^{-5}
1c	**2c**	2.17×10^{-7}	1.74×10^{-7}

[a] Upon mixing 0.125 M halonitrobenzene **1** and 1.25 M amine **2**.

observed in corresponding reactions using methoxide ion as a nucleophile.[7]

For the reaction with 1-fluoro-4-nitrobenzene (**1a**) Fig. 2 clearly shows the expected order in reactivity between the amines **2**: pyrrolidine > piperidine > morpholine,[5,8] having rate enhancements of 2.7, 1.7 and 1.5, respectively at 600 bar. A batch reaction at lab scale, at 1 bar, resulted in k-values comparable to those obtained with the microreactor, thereby excluding microreactor-wall effects.

$$(\partial \ln k/\partial p)_T = -\Delta V^{\neq}/RT \quad (2)$$

The activation volumes were calculated from a plot of the second-order reaction rate constants *versus* pressure using eqn. 2; they are summarized in Table 2. The most negative activation volumes are found for the fastest reactions, *e.g.* the reaction of 1-fluoro-4-nitrobenzene (**1a**) with pyrrolidine (**2a**). All these values are in the same range as those reported in the literature for the aromatic nucleophilic substitution reactions of bromoquinolines and bromonaphthalenes with piperidine.[9]

It is known that nucleophilic aromatic substitution reactions of halonitrobenzenes with secondary amines can be base catalyzed, the amine also being the catalyst.[10] An example is the reaction of 2,4-dinitrohalobenzenes with morpholine,[11] piperidine,[12] and aniline.[9] To investigate this catalytic effect, the reactions of 1-fluoro-4-nitrobenzene (**1a**) with pyrrolidine (**2a**) and piperidine (**2b**) were performed at different amine concentrations. The same approximations by pseudo-first order kinetics as described above were used. Although the approximation is not valid in all cases, meaningful results were still obtained. Plots of the second-order rate constants *vs.* the pyrrolidine or piperidine concentrations pass through the origin and have a positive slope (Fig. 3). This indicates that the reactions are amine catalyzed.[13]

Table 2 Activation volumes $\Delta V^{\neq}$ (cm^3 mol^{-1}) for the reactions of halonitrobenzenes **1a–c** with amines **2a–c**

	Amine[a]		
Halonitrobenzene[a]	Pyrrolidine **2a**	Piperidine **2b**	Morpholine **2c**
1a	−58[b]	−32.4[b]	−22.5
1b	−41.7	−23.3	−18.2
1c	−32.7	−17.3	−14.5

[a] Upon mixing 0.125 M halonitrobenzene **1** and 1.25 M amine **2**. [b] The errors for the reactions of **1a** with **2a** and **1b** with **2b** are 0.4 and 0.1 cm^3 mol^{-1}, respectively, after five different experiments.

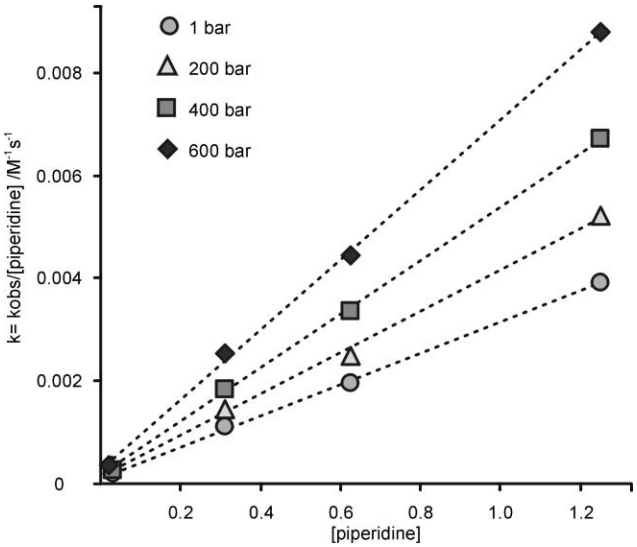


Fig. 3 Piperidine (**2b**) concentration dependence at different pressures for the reaction with 1-fluoro-4-nitrobenzene (**1a**) in THF.

Usually Diels–Alder reactions[14] have rather high negative activation volumes ($\Delta V^{\neq} \approx -25$ to -45 cm^3 mol^{-1}),[15] which make them susceptible to pressure.

Recently, Yuan *et al.*[16] reported that at room temperature the aza Diels–Alder reaction of Danishefsky's diene **4** with imines in methanol gave 2-substituted dihydro-4-pyridone derivatives in good yield. Although the reaction proceeds already at *room temperature*, the reaction of Danishefsky's diene **4** with imine **5** to give 1,2-diphenyl-dihydro-4-pyridone (**6**) (Scheme 1b) in methanol was studied in our set-up at different pressures. The product formation was monitored by the increase of the absorption at 335 nm in the UV/Vis spectrum. A $\Delta V^{\neq}$ of -33 cm^3 mol^{-1} was calculated using eqn. 2. This value is in agreement with those of related Diels–Alder reactions such as *e.g.* the reaction of furan with furan-2,5-dione ($\Delta V^{\neq} = -30.5$ cm^3 mol^{-1}) and 9-(hydroxymethyl)-anthracene with *N*-ethylmaleimide ($\Delta V^{\neq} = -31.4$ cm^3 mol^{-1}).[17]

In conclusion, to the best of our knowledge, this simple set-up is the first example in which a reaction under high pressure can be monitored on-line. In addition, an important advantage of the set-up is that high-pressure reactions can be studied without the extensive safety precautions that are required for conventional high-pressure instrumentation.

M. K. would like to thank Dr Miyoshi (Tokushima Univ., Japan) for kind suggestions. This research is supported by the Technology Foundation STW, applied science division of NWO and the technology program of the Ministry of Economic Affairs.

Fernando Benito-Lopez,[a] Willem Verboom,*[a] Masaya Kakuta,[b] J. (Han) G. E. Gardeniers,*[b] Richard J. M. Egberink,[a] Edwin R. Oosterbroek,[b] Albert van den Berg[b] and David N. Reinhoudt[a]
[a]Laboratory of Supramolecular Chemistry and Technology (SMCT), MESA+ Institute for Nanotechnology, University of Twente, P.O. Box 217, 7500 AE, Enschede, The Netherlands. E-mail: w.verboom@utwente.nl; Fax: +31 (0)53 489 4645; Tel: +31 (0)53 489 2977
[b]BIOS-Lab-on-a-chip group, MESA+ Institute for Nanotechnology, University of Twente, P.O. Box 217, 7500 AE, Enschede, The Netherlands. E-mail: j.g.e.gardeniers@utwente.nl; Fax: +31 (0)53 489 2287; Tel: +31 (0)53 489 4356

Notes and references

1 R. van Eldik and F. G. Klärner, in *High Pressure Chemistry*, eds. R. van Eldik and F. G. Klärner, Wiley-VCH, Weinheim, 2002.
2 *Lab-on-a-chip: Miniaturized systems for (bio)chemical analysis and synthesis*, eds. R. E. Oosterbroek and A. van den Berg, Elsevier, Amsterdam, 2003.
3 S. Bohm, H. van der Linden, A. van den Berg, W. Olthuis and P. Bergveld, *Proc. μTAS 2000 Symp. May 14–18, Enschede, The Netherlands*, Kluwer Academic Publishers, Dordrecht, 2000, p. 611.
4 S. M. Stishov and A. E. Pretova, *Instrum. Exp. Tech.*, 2003, **46**, 719.
5 T. Ibata, Y. Isogami and J. Toyoda, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 42; T. Ibata, M. H. Shang and T. Demura, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 2941.
6 G. Bartoli and P. E. Todesco, *Acc. Chem. Res.*, 1977, **10**, 125.
7 G. P. Brynner, M. Leveris, P. G. Lutz and J. Miller, *J. Chem. Soc.*, 1954, 1265.
8 T. Ibata, X. Zuo and T. Demura, *Tetrahedron Lett.*, 1993, **34**, 5613.
9 K. R. Brower, *J. Am. Chem. Soc.*, 1959, **81**, 3504; K. R. Brower, *J. Am. Chem. Soc.*, 1958, **80**, 2105.
10 T. A. Emokpae and C. Isanbor, *Int. J. Chem. Kinet.*, 2004, **36**, 188; J. F. Bunnett and R. H. Garst, *J. Am. Chem. Soc.*, 1965, **87**, 3875.
11 C. F. Bernasconi and P. Schmid, *J. Org. Chem.*, 1967, **32**, 2953.
12 J. F. Bunnett and C. F. Bernasconi, *J. Org. Chem.*, 1970, **35**, 70.
13 C. Isanbor, T. A. Emakpae and M. R. Crampton, *J. Chem. Soc., Perkin Trans. 2*, 2002, 2019.
14 K. Matsumoto, A. Sera and T. Uchida, *Synthesis*, 1985, 1; K. Matsumoto and A. Sera, *Synthesis*, 1985, 999; M. Ciobanu and K. Matsumoto, *Liebigs Ann. Rec.*, 1997, 623; F. G. Klärner and B. M. Diedrich, in: *The Chemistry of Dienes and Polyenes*, (Z. Rappoport, ed.), Vol. 1, p. 547, Wiley, New York, 1997.
15 J. R. McCabe and C. A. Eckert, *Acc. Chem. Res.*, 1974, **7**, 251; C. Brun, G. Jenner and A. Deluzarche, *Bull. Soc. Chim. Fr.*, 1972, 2332.
16 Y. Yuan, X. Li and K. Ding, *Org. Lett.*, 2002, **4**, 3309.
17 A. Drljaca, C. D. Hubbard, R. van Eldik, T. Asano, M. V. Basilevsky and W. J. Le Noble, *Chem. Rev.*, 1998, **98**, 2167.