Glycosylation in flow: effect of the flow rate and type of the mixer

I. V. Myachin,[a,b] A. V. Orlova,[b] and L. O. Kononov[b,c]★

[a]D. I. Mendeleev University of Chemical and Technology of Russia, 9 Miusskaya pl., 125047 Moscow, Russian Federation
[b]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (499) 135 5328. E-mail: kononov@ioc.ac.ru, leonid.kononov@gmail.com
[c]Moscow Physical Technical Institute (National Research University), 9 Institutsky per., 141701 Dolgoprudnyi, Moscow Region, Russian Federation

The influence of the flow rate and the mode of mixing of reagent solutions on the result of glycosylation of isopropyl alcohol with glycooxazoline in 1,2-dichloroethane in the presence of (±)-camphor-10-sulfonic acid was studied. No reaction products were observed at low flow rates ($\leqslant$0.043 mL h^{-1}) when using two Comet X-01 micromixers. Under these conditions, the disaggregation of supramers of the reagents is apparently inefficient for the reaction between them to occur. However, when one of the Comet X-01 micromixers was replaced with a T-shaped adapter (at the same flow rate), the expected reaction products, glycoside and glycal, appeared in the reaction mixture. This apparently suggests a higher disaggregation of the supramers reagents under these conditions, which allows the chemical reaction between them to occur.

Key words: glycosylation in flow, glycooxazoline, oxazoline method, Comet X-01 micromixer, supramers.

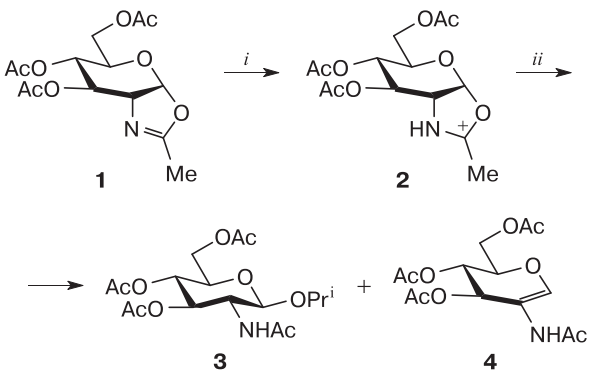
Two fundamentally different methods for performing chemical reactions in solutions are known: in a batch reactor (in a flask) and in a flow type reactor (in flow).[1—8]

It has recently been shown that the type of reactor can affect the yields of products and stereoselectivity of glycosylation (flow reactors of various design were compared with the batch reactor (flask)).[9,10] However, the influence of the flow rate on the result of glycosylation in flow [8—14] was not studied earlier. We decided to fill this gap and during this study unexpectedly obtained unprecedented results, which are described below.

The influence of the flow rate on the result of glycosylation in the flow reactor was studied using glycosylation[15—18] of isopropyl alcohol with glycooxazoline **1**[16,19] in 1,2-dichloroethane (DCE)[18,20—22] in the presence of (±)-camphor-10-sulfonic acid (CSA)[23,24] as an example (Scheme 1).

A system consisting of two **M1** and **M2** mixers (see Fig. 1) was used as a flow reactor. The system makes it possible to mix reagents at various temperatures (the conditions are shown in Scheme 1). In this work, solutions of oxazoline **1** and CSA in DCE were mixed in the **M1** mixer at room temperature (~20 °C). The obtained solution was further supplied *via* a capillary to the **M2** mixer, where it was mixed at 80 °C with a solution of isopropyl alcohol in DCE. The solution coming out from the **M2** mixer *via* a capillary-reactor went into a receiving flask with a solution of Pr^i_2NEt in toluene (see Fig. 1), where the reaction was quenched.

Scheme 1



Reagents and conditions: *i*. CSA, DCE, T = 20 °C, mixer **M1**; *ii*. Pr^iOH, DCE, T = 80 °C, mixer **M2** (Fig. 1).

After reaction termination, the compositions of the reaction mixtures were analyzed by ^{13}C NMR spectroscopy. When two identical Comet X-01 micromixers[14] were used as the **M1** and **M2** mixers, the amount of the reaction products, isopropyl glycoside **3** and glycal **4***, changed with an increase in the flow rate in a complicated manner, in particular, it decreased (Fig. 2, Table 1) at high

* A low conversion of oxazoline **1** under these conditions should be mentioned.

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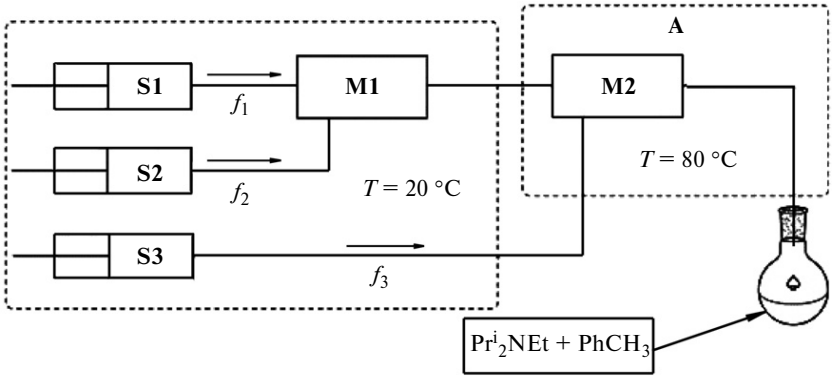

Fig. 1. Scheme of the flow reactor in which glycosylation was conducted; **A** is the bath. Syringes **S1** (solution of **1** in DCE), **S2** (solution of CSA in DCE), and **S3** (solution of Pr^iOH in DCE) were used to pump the solutions of the reagents through the **M1** and **M2** mixers. Flow rate $f = f_1 = f_2 = f_3$.

flow rates (⩾0.4 mL h^{-1}). Note that products **3** and **4** were completely absent at low flow rates (0.03 and 0.043 mL h^{-1}). In this case, only unreacted oxazoline **1** was found in the receiving flask (Fig. 3, *a*, Table 1).

A decrease in the amount of the reaction products at the rates higher than 0.4 mL h^{-1} can be explained by insufficient duration of contact between the reactants (*i.e.*, the reaction has no time to complete). At the same time, in a range of low flow rates and, as a consequence, of a longer duration of contact between the reactants (residence time ~30 h, *i.e.*, nearly under static conditions: almost as in the flask), the absence of products of transformation of acid-labile[25] oxazoline **1** looks very unusual. Moreover, the expected reaction products **3** and **4** were observed in the reaction mixture (Fig. 3, *b*) at a flow rate of 0.03 mL h^{-1} when a T-shaped adapter (instead of a Comet X-01 micromixer) was used as the **M1** mixer. This unexpected result is consistent with the earlier found[9,10,26] data on the influence of the mode of mixing of reagents on the results of chemical reactions conducted in flow.

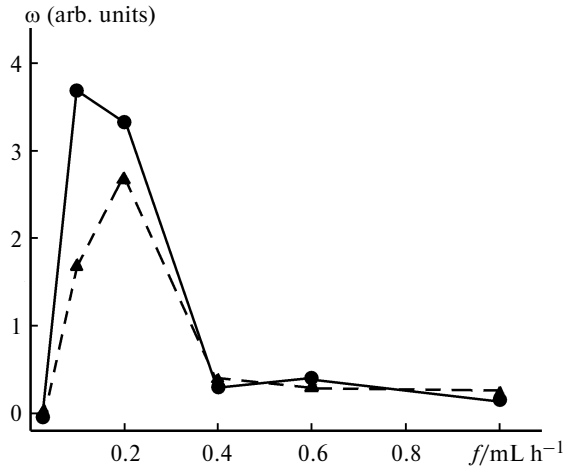

Fig. 2. Amounts (ω) of glycoside **3** (dashed line) and glycal **4** (solid line) at various flow rates (*f*); **M1** = **M2** = Comet X-01 micromixer (see Scheme 1, Fig. 1, and Table 1).

In our opinion, this phenomenon can be described in terms of the model of structure of solutions proposed by M. Sedlák.[27—29] The model assumes that the solution contains domains — long-lived supramolecular aggregates (supramers[26]) containing molecules of the solute and solvent. The use of this model for the reaction solution shows[26] that the product cannot be formed from reagent molecules located inside the domains of the solution, since they are unable to contact each other. The product is formed from the molecules located on the surface of domains or between them. Therefore, to achieve high yields of the product, one should destroy domains (supramers) of the reagents, which are sensitive to mechanical impact[26] and, hence, can partially or completely decompose under "mild" impact. It was predicted[26] on the basis of this hypothesis that the mode of mixing of solutions of reagents can influence the structure of supramers of reagents and, hence, their macroscopic reactivity.

In the framework of the considered model, it can be assumed that at low flow rates (⩽0.043 mL h^{-1}) and using two Comet X-01 micromixers (see Fig. 3, *a*) the disag-

Table 1. Amounts of glycoside **3** and glycal **4** (ω) at various flow rates (*f*) (also see Fig. 2)

f/mL h^{-1}	ω (arb. units)	
	3	**4**
0.03	0	0
0.043	0	0
0.1	1.67	3.67
0.2	2.66	3.33
0.4	0.38	0.33
0.6	0.30	0.35
1	0.22	0.17

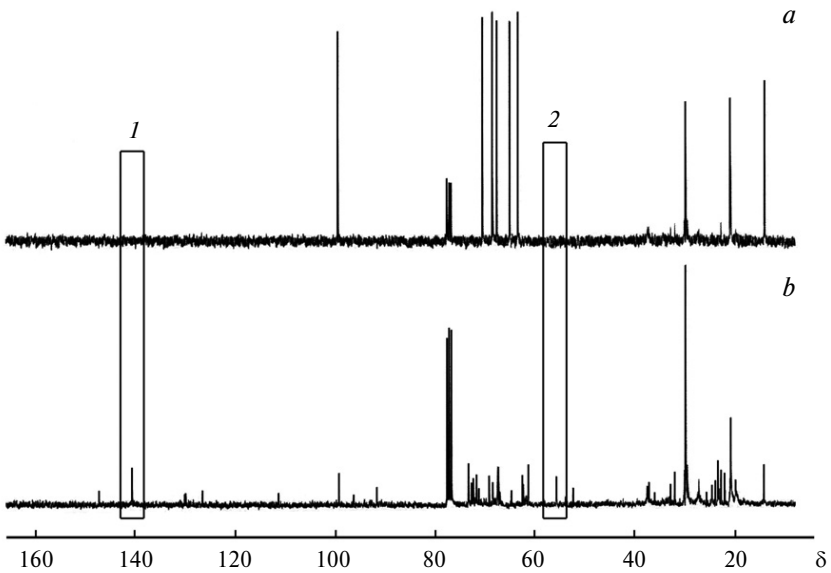

Fig. 3. ^{13}C NMR spectra of the reaction mixtures obtained by using different **M1** mixers and the same flow rate (f = 0.03 mL h^{-1}): (*a*) **M1** = **M2** = Comet X-01 micromixer; (*b*) **M1** = T-shaped adapter, **M2** = Comet X-01 micromixer (see Scheme 1 and Fig. 1); *1*, signal of the C(1) atom of glycal **4** (δ_C 140.6) and *2*, signal of the C(2) atom of isopropyl glycoside **3** (δ_C 55.8).

gregation of supramers of reagents is inefficient for the reaction between them to occur. Apparently, tight[30] supramers of oxazoline **1** or acid (CSA)* (*cf.* studies of the supramolecular structuring of solutions of acids[31—33]) are formed under these conditions, and the access of the CSA molecule to the reaction center of oxazoline **1** is impeded in these supramers, which is manifested as an enhanced stability of oxazoline **1** under the action of acid. In the case of replacement of the **M1** mixer with a T-shaped adapter (at the same flow rate), the formation of reaction products **3** and **4** seems to indicate a higher disaggregation of the supramers of the reagents under these conditions, which makes the chemical reaction between them possible.

Thus, in this work, we experimentally observed the earlier predicted[26] effect of the flow rate and mode of mixing of solutions of reagents on their reactivity and advanced a rational explanation of the found facts based on the application of the supramer approach.[26]

Experimental

The system of the **M1** and **M2** mixers (Teflon (PTFE) Comet X-01 micromixer or a T-shaped adapter (Tee Assembly Tefzel™ (ETFE), for 1/16" (IDEX Health & Science LLC, www.idex-hs.com)) was used for the reactions in flow assembled as shown in Fig. 1 using Teflon (PTFE) capillary and connecting unions. Internal diameters of all capillaries were 1.0 mm. The length of the capillaries between **S1**—**M1**, **S2**—**M2**, and **M1**—**M2** was 0.40 m, that between **S3**—**M2** was 1.00 m, and the length of the outlet capillary was 0.75 m. Solutions were pumped using an AL-1200 multichannel syringe pump (World Precision Instruments, www.wpiinc.com). ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument (300.13 and 75.47 MHz, respectively) at 303 K. Anhydrous 1,2-dichloroethane (DCE, distilled in an argon atmosphere over P_2O_5 and then over CaH_2 and kept over molecular sieves 4 Å under argon) was used for glycosylation. Propan-2-ol (Pr^iOH) was distilled in argon over CaO and kept over molecular sieves 4 Å under argon. A solution of oxazoline **1** (see Ref. 19) (60 mmol L^{-1}) in DCE was prepared by the dissolution of a dried *in vacuo* (for 2 h at 0.15 mbar) sample of oxazoline **1** (296 mg, 0.9 mmol) in DCE (15 mL). A solution of CSA (25 mmol L^{-1}) in DCE was prepared by the dissolution of a weighed sample of CSA (5.2 mg, 22.5 μmol) in DCE (15 mL). A solution of propan-2-ol (180 mmol L^{-1}) in DCE was prepared by adding Pr^iOH (207 μL, 2.7 mmol) to DCE (15 mL). All solutions were kept for not more than 2 weeks and replaced with fresh solutions as they were spent out. Syringes (nominal volume 5 mL, material polypropylene; Becton, Dickinson & Co., www.bd.com) were filled with gaseous argon in an amount sufficient for the complete displacement of all liquid from the flow system along with solutions of the reagents. The contents of the syringes were as follows: syringe **S1**: 3 mL of a solution of oxazoline **1** in DCE (60 mmol L^{-1}) and 1 mL of argon; syringe **S2**: 3 mL of a solution of CSA in DCE (25 mmol L^{-1}) and 1 mL of argon; and syringe **S3**: 3.5 mL of a solution of Pr^iOH in DCE (180 mmol L^{-1}) and 0.5 mL of argon. The **M1** mixer was at room temperature (~20 °C), and the **M2** mixer was heated in a glycerol bath (the temperature of the bath was 80 °C). A capillary-reactor (internal diameter 1.0 mm, length 0.75 m) was placed at the outlet of the **M2** mixer. The solution coming from the capillary-reactor was supplied at ~20 °C to a receiving flask (50 mL) containing a solution of Pr^i_2NEt (150 μL, 0.86 μmol, 11.5 equiv. based on CSA) in $PhCH_3$ (2 mL). After the completion of pumping solutions of all reagents through

* Amphiphilic CSA molecules in nonpolar 1,2-dichloroethane might form supramers structurally similar to reverse micelles in which the acidic moiety is shielded from the solution with other reagents, which decreases the reactivity of CSA.

the system, the solution in the receiving flask was diluted with dichloromethane (25 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (30 mL) and then with water (30 mL). The organic phase concentrated at a reduced pressure on a rotary evaporator, and the residue was dried for 3 h *in vacuo* (0.15 mbar), after which it was dissolved in $CDCl_3$ (0.6 mL) and analyzed by ^{13}C NMR spectroscopy. Each experiment was carried out once. The amounts of products **3** and **4** in the reaction mixture (see Fig. 2 and Table 1) are indicated in arbitrary units (ω) equal to the ratios of the intensities of the characteristic peaks in ^{13}C NMR spectra of isopropyl glycoside **3** (δ_C 55.8, C(2)) and glycal **4** (δ_C 140.6, C(1)) to the intensity of the peak of the initial oxazoline **1** (δ_C 14.0, CH_3 at the C(2) atom of the oxazoline ring). The NMR spectra of compounds **1**,[34,35] **3**,[36] and **4** (see Ref. 34) coincide with the published data.

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