Reversibility of the [2 + 2] Cycloaddition of Isocyanates to Glycals

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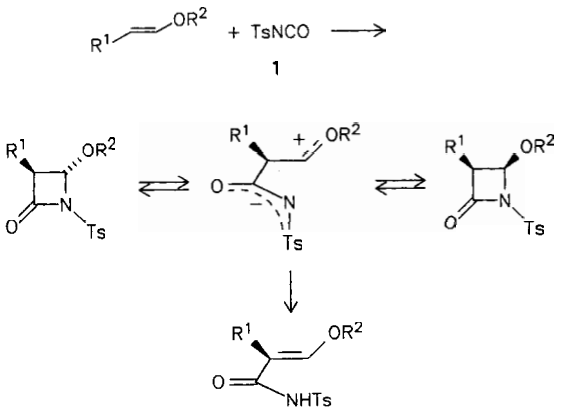
[2 + 2] Cycloadducts obtained by the addition of tosyl isocyanate to glycals (**10**–**13**) undergo retro-addition upon heating or even at room temperature. The rate of retro-addition increases with rising temperature and polarity of the solvent.

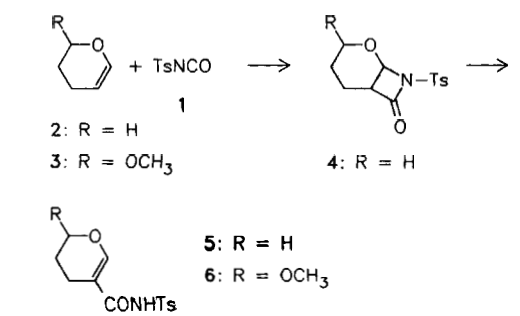
[2 + 2] Cycloaddition of tosyl isocyanate (**1**) to vinyl ethers has been studied by Effenberger's group in detail[1,2]. Concerted formation of the four-membered β-lactam ring and a stepwise reaction proceeding via a zwitterionic intermediate for epimerization at C-4 or for rearrangement to the α,β-unsaturated amide have been proposed (Scheme 1).

Scheme 1



According to these authors[2] the reaction of **1** with 3,4-dihydro-2*H*-pyran (**2**) at low temperature (0°C) leads to the formation of bicyclic β-lactam **4**; elevation of the temperature of the cyclization reaction causes a rearrangement of the four-membered ring to the open-chain amide **5**[2]. Similarly, Chan and Hall[3] have found that 3,4-dihydro-2-methoxy-2*H*-pyran (**3**) reacts with **1** to give unsaturated amide **6**, but no β-lactam has been found (Scheme 2).

Scheme 2

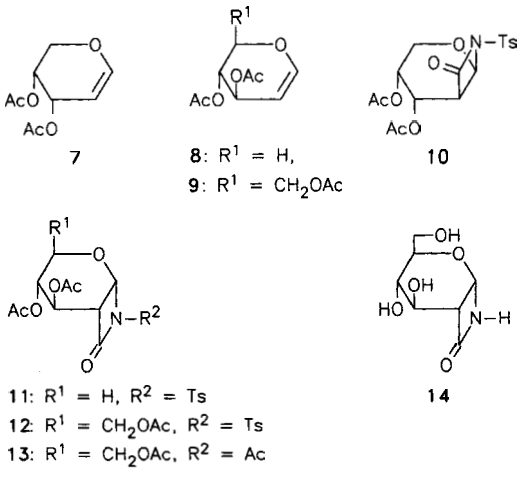


In contrast, tri-*O*-acetyl-D-glucal, which consists of an optically pure 2,3,4-trisubstituted 3,4-dihydro-2*H*-pyran, has been found to remain unreactive on treatment with chlorosulfonyl isocyanate[4]; isocyanate acts as an acid catalyst causing decomposition of the sugar.

Our high-pressure experiments[5,6] using acetylated glycals and tosyl isocyanate (**1**) have shown that these reactions are under thermodynamic control of product formation and may proceed at atmospheric pressure under specific conditions, including an excess of isocyanate, as well as proper selection of solvent and substrates[7–9].

In this paper we reconsider the reversibility of [2 + 2] cycloaddition of isocyanates to vinyl ethers. The tendency of the cycloadducts towards retroaddition explains why the first attempts at [2 + 2] cycloaddition of sulfonyl isocyanates to glycals under thermal conditions have been unsuccessful[4,10]. Moreover, for reactions proceeding by a concerted mechanism[11] this generally obvious fact sheds a new light on the mechanism of this reaction, proposed by Effenberger et al.[1]

For the present study, we have selected as model compounds **4**, three adducts of the β-D-*arabino* **10**, α-D-*xylo* **11**, α-D-*gluco* configuration **12**, and *N*-acetyl-β-lactam **13** of the α-D-*gluco* configuration. Compounds **10**–**12** have been obtained at high pressure from the respective glycals **7**–**9**, whereas **13** has been prepared by acetylation of the β-lactam **14**. The composition of the reaction mixture has been determined at intervals by ^{1}H-NMR analysis; the reactions have been performed in NMR test tubes[8,9].



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At atmospheric pressure and room temperature adduct **12** undergoes retroaddition to afford the starting glucal. The rate of retroaddition increases with rising temperature and polarity of the solvent. At room temperature in $CDCl_3$ solution D-glucal **9** is formed only after 24 h (Table 1). The time dependence of the reaction mixture composition at 70°C in C_6D_6 for adducts **10**, **11**, and **12** is presented in Figure 1. The rate of retroaddition depends on the structure and configuration of the substrate. The pentopyranoid β-D-*arabino* compound **10** undergoes the retroreaction faster than the α-D-*xylo* isomer **11**, and the latter faster than its hexopyranoid homologue of the α-D-*gluco* configuration **12** (Figure 1). This sequence of reactivity can be explained by a participation of the neighboring 3-*O*-acetyl substituent which in the transition state occupies an antiperiplanar position thus facilitating the retroaddition. Owing to the conformational preferences the inclination to adapt such an arrangement changes in the order β-D-*arabino*, α-D-*xylo*, α-D-*gluco*. The addition of *tert*-butyl alcohol to the reaction mixture as isocyanate scavenger increases the rate of glycal formation owing to termination of the [2 + 2] cycloaddition.

Table 1. Composition of the reaction mixture as a function of time for the retroaddition of 3,4,6-tri-*O*-acetyl-2-*C*:1-*N*-carbonyl-2-deoxy-*N*-(tolylsulfonyl)-α-D-glucopyranosylamine (**12**)

	$CDCl_3$ solution		CD_3CN solution	
	Temperature 20°C			
Time	**9** (%)	**12** (%)	**9** (%)	**12** (%)
24 h	10.5	89.5	18.5	81.5
72 h	15.0	85.0	40.0	60.0
144 h	23.6	76.4	55.7	44.3
	Temperature 60°C			
	9 (%)	**12** (%)	**9** (%)	**12** (%)
15 min	11.9	88.1	21.7	78.3
45 min	20.6	79.4	41.7	58.3
90 min	28.0	72.0	62.9	37.1
24 h	100.0	–	100.0	–

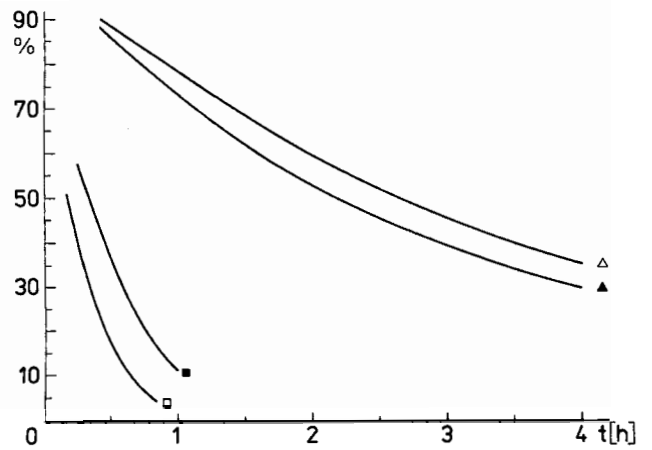


Figure 1. The time dependence of the content of cycloadducts **10**, **11**, and **12** (0.1 mmol) in C_6D_6 solution (0.5 ml), at 70°C. □: **10**; ■: **11**; △: **12**; ▲: **12** and *tert*-butyl alcohol (0.2 mmol)

Reexamination of the rearrangement of the adduct **4** by Effenberger and Gleiter[2] has afforded interesting results. Pure adduct **4**, recrystallized at low temperature and dissolved in benzene, shows at room temperature after 20 min the presence of about 10% of dihydro-2*H*-pyran **2**. Heating of the mixture to 70°C causes after 20 min precipitation of the α,β-unsaturated amide **5**, whereas in benzene solution almost only 3,4-dihydro-2*H*-pyran (**2**) and tosyl isocyanate (**1**) are present. The content of the adduct **4** is below 5%. Upon prolongation of heating, the content of precipitate **5** increases slowly, and finally **5** is the only product.

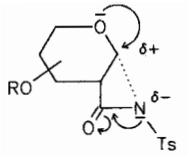
The tetraacetate **13** undergoes retroaddition in boiling trichlorobenzene; after 3 h, D-glucal **9** is recovered in about 45% yield. The high temperature applied in the experiment causes decomposition of the glucal **9** formed, leading to a decrease of the yield of the retroaddition product.

In the light of the literature data[1,2,5–9] and of our experiments, free energies of activation of the cycloaddition, of the reverse reaction, and of the rearrangement to the corresponding α,β-unsaturated amide do not differ considerably. Hence, a slight modification of the glycal moiety or even a change in the solvent can shift the reaction towards the desired [2 + 2] cycloadduct or subsequently towards the respective unsaturated amide. In the case of adducts **10**–**12** derived from acetylated glycals and tosyl isocyanate (**1**), the glycal is more stable than the adduct, whereas the energy of activation of the rearrangement to the α,β-unsaturated amides is relatively higher than that leding to the starting sugar (**7**–**9**). The application of high pressure stops the retroaddition, whereas the rearrangement to the amide, representing an intramolecular process, is not accelerated. The reaction can be shifted towards the α,β-unsaturated amide only if high pressure and higher temperature are applied[5,6]. Consequently, at high pressure the cycloadduct can be obtained in a good yield.

At atmospheric pressure, in the retroreaction experiment only glycal and tosyl isocyanate are formed. Upon prolonged heating, the respective α,β-unsaturated amide is not formed, and eventually the glycal slowly undergoes decomposition.

In the case of the cycloadduct derived from 3,4-dihydro-2*H*-pyran (**2**), at room or higher temperature the situation is similar, but the energy of activation of rearrangement is somewhat lower. This fact and the higher thermal stability of the dihydro-2*H*-pyran, in comparison with acetylated glycals, play a decisive role in the formation of the α,β-unsaturated amide.

The relationship between the rate of cycloaddition and that of the retroreaction on the one hand and the polarity of the solvent on the other hand strongly suggest the presence of a polar transition state **15** or of a polar intermediate such as zwitterion **16**. The stereospecificity of the [2 + 2] cycloaddition of tosyl isocyanate (**1**) to *cis*- and *trans*-vinyl ethers has convinced Effenberger's group[1,2] that a concerted process is involved. Our experiments strongly support this opinion.



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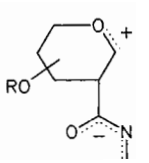

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Experimental

^1H NMR: Bruker AM 500 and Varian Gemini 200. – Optical rotations: Jasco Dip-360 digital polarimeter.

Compound **4** was obtained according to the Effenberger and Gleiter procedure[2], whereas compounds **10**, **11**, and **12** were syn-

thesized at 12-kbar pressure and room temperature in ethyl ether solution according to our earlier procedure[6].

3,4-Di-O-acetyl-2-C: 1-N-carbonyl-2-deoxy-N-(p-tolylsulfonyl)-β-D-arabino-pyranosylamine **10**: Yield 90%, m.p. 100–101 °C, $[\alpha]_D$ = −150.0 (*c* = 2, in dichloromethane). – IR (nujol): $\tilde{\nu}$ = 1750 cm^{-1} (OAc), 1820 (C=O). – ^1H NMR ($CDCl_3$): δ = 2.05, 2.08 (2 s, 6H, 2 Ac), 2.47 (s, 3H, Ts), 3.44 (t, $J_{1,2}$ = 5.3, $J_{2,3}$ = 5.2 Hz, 1H, 2-H), 3.58 (dd, $J_{5,5'}$ = 11.8, $J_{4,5}$ = 2.6 Hz, 1H, 5-H), 3.85 (dd, $J_{4,5'}$ = 4.0 Hz, 1H, 5'-H), 5.13 (dt, 1H, 4-H), 5.26 (dd, $J_{3,4}$ = 4.1 Hz, 1H, 3-H), 5.83 (d, 1H, 1-H), 7.38, 7.90 (2 m, 4H, Ts).

$C_{17}H_{19}NO_2S$ (397.4) Calcd. C 51.38 H 4.82 N 3.52
Found C 51.1 H 4.6 N 3.5

N-Acetyl-3,4,6-tri-O-acetyl-2-C: 1-N-carbonyl-2-deoxy-α-D-glucopyranosylamine (**13**): β-Lactam **14** (0.19 g, 1 mmol) in pyridine (5 ml) was treated with 4-(dimethylamino)pyridine (0.01 g) and acetic anhydride (1 ml). After the disappearance of the substrate (about 30 min), the acetylating agents were removed in vacuo. The crude mixture was dissolved in dichloromethane and the solution passed through a Florisil column. Subsequently, the solvent was evaporated from the eluate, and the crude product was recrystallized from hexane/ethyl acetate to afford **13** (0.299 g, 80%); m.p. 118–119 °C, $[\alpha]_D$ = +100.3 (*c* = 2, in dichloromethane). – IR (nujol): $\tilde{\nu}$ = 1740 cm^{-1} (OAc), 1810 (C=O). – ^1H NMR ($CDCl_3$): δ = 2.07, 2.08, 2.11 (3 s, 9H, 3 Ac), 2.41 (s, 3H, NAc), 3.57 (m, $J_{1,2}$ = 5.3, $J_{2,3}$ = 2.5, $J_{2,4}$ = 0.9 Hz, 1H, 2-H), 4.06 (m, 1H, 5-H), 4.20 (dd, 1H, $J_{6,6'}$ = 11.9, $J_{5,6}$ = 3.8 Hz, 6-H), 4.32 (dd, $J_{5,6'}$ = 5.6 Hz, 6'-H), 5.02 (m, 1H, 4-H), 5.38 (dd, 1H, $J_{3,4}$ = 4.8 Hz, 1H, 3-H), 5.88 (d, 1H, 1-H).

$C_{15}H_{19}NO_9$ (375.3) Calcd. C 50.42 H 5.36 N 3.92
Found C 50.4 H 5.4 N 4.0

Reversibility experiments were performed in an NMR test tube as follows. A solution of the adduct (0.1 mmol) in $CDCl_3$ or CD_3CN or else C_6D_6 (0.5 ml) in an NMR test tube was kept at room temp., 60 or 70 °C. The components of the reaction mixture was characterized by the chemical shift of the 1-H proton. The compositions of the reaction mixture as a function of time were determined approximately by integration of the appropriate signals of 1-H; they are presented in Table 1 and graphically in Figure 1.

Retroaddition of **13**: A solution of β-lactam **13** (0.072 g, 0.2 mmol) in 1,2,4-trichlorobenzene (2 ml) was kept under reflux for 3 h. Subsequently, the mixture was cooled and the solvent evaporated in vacuo. The residue was purified on silica gel to give tri-*O*-acetyl-D-glucal (**9**, 0.024 g, 45%).

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