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Solvent Effects in the Nucleophilic Substitutions of Tetrahydropyran Acetals Promoted by Trimethylsilyl Trifluoromethanesulfonate: Trichloroethylene as Solvent for Stereoselective *C*- and *O*-Glycosylations

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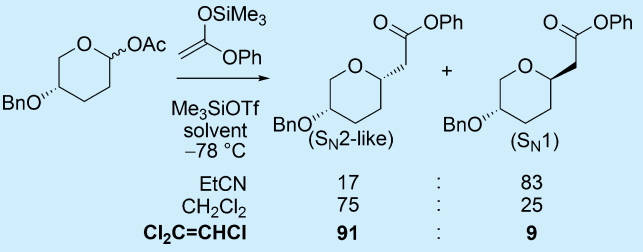
Supporting Information

ABSTRACT: The selectivities of nucleophilic substitution reactions of tetrahydropyran acetals promoted by trimethylsilyl trifluoromethanesulfonate depend upon the reaction solvent. Polar solvents favor the formation of S_N1 products, while nonpolar solvents favor S_N2 products. Trichloroethylene was identified as the solvent most likely to give S_N2 products in both *C*- and *O*-glycosylation reactions.

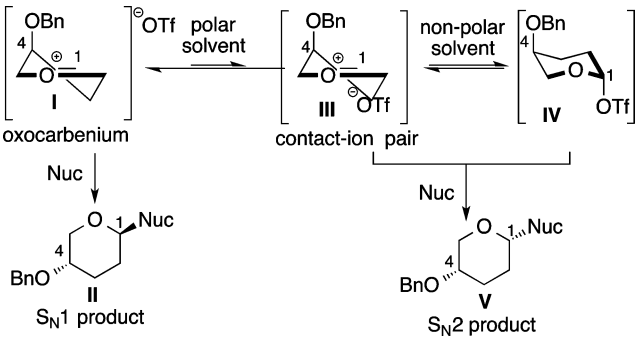


Controlling the mechanism of nucleophilic substitution reactions of acetals is an important challenge in carbohydrate chemistry because which mechanistic pathway is followed determines the stereochemical outcome of the reaction.[1] The use of activators such as trifluoromethanesulfonic acid (triflic acid), triflic anhydride, and trimethylsilyl triflate (Me_3SiOTf) has been particularly useful because the resulting glycosyl triflate intermediates undergo S_N2-like substitutions, leading to reactions with predictable stereochemical outcomes.[2] The S_N2 reactions of glycosyl triflates exhibit considerable S_N1 character,[3] and in many cases, these substrates also react via oxocarbenium ions, which result in diminished selectivity.[4,5] Careful manipulation of reaction parameters, including the choice of protecting groups on the glycosyl donor,[2,3,6−8] glycosyl acceptor,[8−10] and additives,[11] is crucial to minimize the interference of the S_N1 pathway and thus maximize stereoselectivity through the S_N2 mechanism. The selectivity of glycosylation reactions involving glycosyl triflates can also vary depending upon solvent, with dichloromethane, diethyl ether, and toluene used most commonly.[3,6,11−20]

Here, we provide evidence that the choice of solvent determines partitioning between the two reaction pathways, S_N2 and S_N1, for reactions in the presence of triflate. These studies reveal that trichloroethylene can dramatically increase the diastereoselectivity of *C*-glycosylation reactions that follow the S_N2 mechanism (in one case, from 75:25 in CH_2Cl_2 to 91:9 in trichloroethylene). Trichloroethylene also increased the selectivity of an *O*-glycosylation reaction, suggesting further application of this solvent in carbohydrate synthesis.

The nature of the solvent should control which mechanism of acetal substitution occurs. The concept is illustrated for a 4-benzoyloxy-substituted tetrahydropyran substrate in the presence of triflate ion (Scheme 1).[21,22] In polar solvents, the free oxocarbenium ion **I** would be favored,[23] leading to the formation of 1,4-trans product **II** in the most polar solvents. In particularly nonpolar solvents, the oxocarbenium/triflate contact-ion pair **III**[21] or axial triflate **IV** would be favored[1,11] because the oxocarbenium ion should be destabilized.[24] Reactions of these intermediates would favor formation of the 1,4-cis product **V**.[25]

Scheme 1. Possible Intermediates Leading to Substitution Products



To test these ideas about how the mechanism could be controlled by the choice of solvent, several experiments were performed in which the acetals, nucleophiles, and solvents were varied. Substitution reactions with a nucleophile/electrophile combination that yielded poor selectivity in the presence of triflate ion were chosen as a baseline to ensure solvent effects would be most apparent (Scheme 2).[21] *C*-Nucleophiles were chosen because their reactions are kinetically controlled, and the nucleophilicity of these substrates can be systematically increased or decreased to study trends in selectivity.[26] Nineteen solvents were examined, with preference given based on the solvent's

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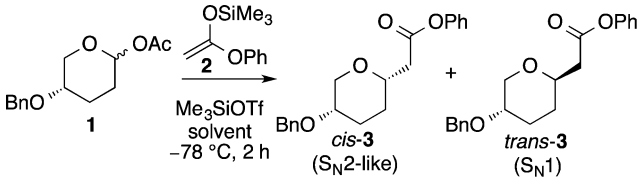
Scheme 2. Nucleophilic Substitutions of Acetal 1



commercial availability, price, volatility (or general ease of isolation of products), substrate solubility, and polarity. Although there is no universal polarity scale, the dipole moment (μ) was used as a general indicator of polarity.[27,28] Nine of the solvents, spanning a range of polarity, gave substitution products in 2 h at −78 °C. Several solvents that were examined (Nujol, pentane, hexane, heptane, cyclopentane, cyclohexane, 2,2,4-trimethylpentane, acetone, 2-butanone, 1-butyl-3-methlimidazolium triflate) either gave poor reactivity or did not meet the criteria of commercial availability and substrate solubility.

As anticipated, the substitution reactions of acetal **1** with silyl ketene acetal **2** were sensitive to solvent polarity (Scheme 2 and Table 1).[27] Highly polar solvents, such as nitriles, favored the formation of the 1,4-trans product *trans*-**3** (entries 10−12), which is likely formed from solvent-separated ions through an S_N1 mechanism (Scheme 1). In contrast, the use of CH_2Cl_2, a commonly used solvent for glycosylation reactions, afforded the 1,4-cis product (the S_N2 product), although the reaction was not selective (75:25, entry 6). Low-polarity solvents such as toluene led to higher selectivity for the 1,4-cis product *cis*-**3**, likely through an S_N2-like mechanism on the triflate **IV** or the contact-ion pair **III** (entry 2).[29] Higher reaction temperatures caused an overall decrease in selectivity (entry 3).[30] Addition of exogenous triflate to promote the formation of the oxocarbenium/triflate contact-ion pair was counterproductive, instead increasing the formation of *trans*-**3** (entries 7 and 12). This outcome is likely caused by the ions increasing the polarity of the solvent, favoring ion pair dissociation.[11,31] The selectivities of these reactions correlated more closely with the solvent's dipole moment, whereas dielectric constant values and empirical solvent parameters show little correlation.[32,33]

Table 1. Influence of Solvent on the Nucleophilic Substitution Reaction of Tetrahydropyran Acetal 1

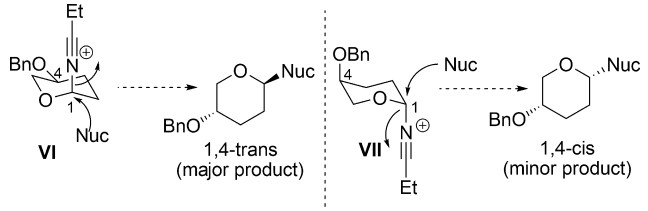
entry	solvent	μ^a	ε^b	$E_T(30)^c$	cis:trans ratio[d]
1	CS_2	0	2.6	32.8	78:22
2	PhMe	0.37	2.38	33.9	88:12
3	PhMe (−20 °C)	0.37	2.38	33.9	64:36
4	**Cl_2C=CHCl**	**0.8**	**3.4**	**35.9**	**91:9**
5	Et_2O	1.15	4.33	34.5	65:35
6	CH_2Cl_2	1.6	8.93	40.7	75:25
7	CH_2Cl_2[e]	1.6	8.93	40.7	68:32
8	THF	1.75	7.58	37.4	55:45
9	EtOAc	1.78	6.02	38.1	37:63
10	H_2C=CHCN	3.87	37.5	46.7	17:83
11	EtCN	4.05	27.7	43.6	21:79
12	EtCN[e]	4.05	27.7	43.6	17:83

[a]Dipole moment (debye). [b]Dielectric constant (F/m). [c]Empirical solvent polarity parameter (kcal/mol). [d]Ratio determined by gas chromatography (GC) and confirmed by ^{1}H NMR spectroscopy. [e]1 equiv of Bu_4NOTf was added.

The highest selectivity for the S_N2 product (*cis*-**3**) was observed when the nonpolar halogenated solvent trichloroethylene was used. The decrease in solvent polarity on changing from CH_2Cl_2 to trichloroethylene increased diastereoselectivity from 75:25 to 91:9 (entries 6 and 4, respectively). Trichloroethylene proved to be a convenient solvent because of its low boiling point (87 °C), low viscosity, low reactivity under these conditions, and modest cost.[34] Despite being a common industrial solvent, trichloroethylene has not been widely adopted in organic reactions,[35−38] although it is useful as a synthetic precursor to alkynes.[39−42] Handling of trichloroethylene should be performed with appropriate safety precautions because its health effects are similar to those of CH_2Cl_2.[43]

Evidence for solvent participation was not observed in these systems. If the solvent were indeed participating,[44] substitution would require reaction of the nitrilium intermediate **VI** to form the observed 1,4-trans product (Scheme 3). Even if this intermediate were formed, its formation is reversible.[45] In the presence of an alkoxy group at C4, however, 1,4-trans nitrilium **VII**[46] should be the favored intermediate.[47−49] Substitution of **VII**, which resembles triflate intermediate **IV** (Scheme 1), would lead to the 1,4-cis product, which is the minor product observed in reactions with propionitrile and acrylonitrile. Consequently, attributing different roles of nitriles than as participating solvents better accommodates the results with polar solvents.[50,51]

Scheme 3. Reaction Intermediates for Solvent Participation



A similar trend in diastereoselectivity as a function of solvent polarity was observed for 5-benzyloxymethyl acetal **4** (Scheme 4 and Table 2). In this case, the alkoxy group is less electron-withdrawing than in the 4-benzyloxy system, and it has a small preference for the equatorial position.[52] Consequently, ionization of the triflate occurs more readily, leading to more S_N1 product (*trans*-**6**). The reaction is only selective in highly polar solvents, suggesting that addition of the reactive nucleophile approaches the diffusion rate limit[46,53] when the oxocarbenium ion is not stabilized by a polar solvent. The proportion of the S_N2 product *cis*-**6** increases with decreasing solvent polarity, as would be expected, with trichloroethylene exhibiting the greatest preference for the 1,5-cis product (entry 2). When a nucleophile strong enough to react with both the anomeric triflate and the contact-ion pair was employed, such as the more reactive alkyl-substituted ketene acetal **5**,[26] more S_N2 product was observed. The modest selectivity (approximately 75:25) and similar

Scheme 4. Nucleophilic Substitutions of Acetal 4

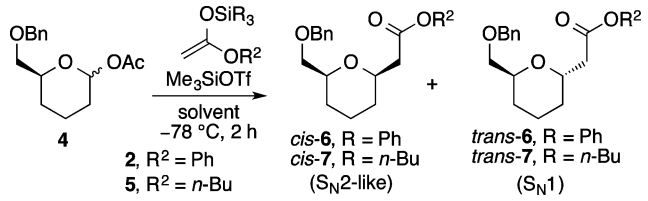


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Table 2. Influence of Solvent on the Nucleophilic Substitution Reaction of Acetal 4

entry	solvent	nucleophile	μ^a	cis:trans ratio[b] (yield, %)[c]
1	PhMe	**2**	0.37	30:70
2	**Cl_2C=CHCl**	**2**	**0.8**	**48:52 (85)**
3	Et_2O	**2**	1.15	18:82
4	CH_2Cl_2	**2**	1.6	40:60 (85)
5	THF	**2**	1.75	6:94
6	EtCN	**2**	4.05	15:85
7	PhMe	**5**	0.37	60:40
8	**Cl_2C=CHCl**	**5**	**0.8**	**73:27**[d]
9	Et_2O	**5**	1.15	48:52[d]
10	CH_2Cl_2	**5**	1.6	77:23[d]
11	THF	**5**	1.75	29:71[d]
12	EtOAc	**5**	1.78	48:52[d]
13	EtCN	**5**	4.05	45:55[d] (57)

[a]Dipole moment (debye). [b]Ratio determined by GC and confirmed by ^{1}H NMR spectroscopy. [c]Combined isolated yield. [d]Product ratios were confirmed by ^{13}C NMR spectroscopy.[56]

selectivities between nonpolar solvents in reactions of acetal **4** may indicate that the glycosyl triflate exists as a mixture of stereoisomers.[54] Furthermore, the product ratio need not reflect the ratio of triflate stereoisomers if they were in rapid equilibrium.[55]

Increased preference for formation of the S_N2 product was observed for substitution reactions of a 2-deoxysugar derivative when low polarity solvents were used (Scheme 5 and Table 3).

Scheme 5. Nucleophilic Substitutions of Acetal 8

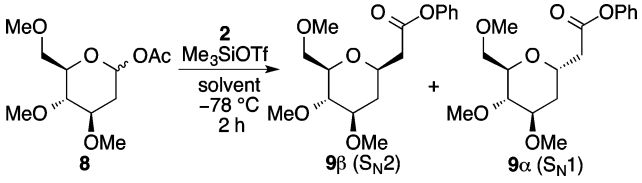


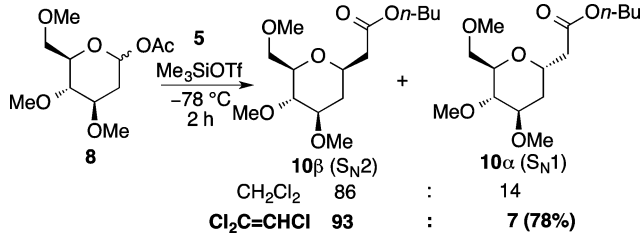
Table 3. Influence of Solvent on the Nucleophilic Substitution Reaction of Acetal 8

entry	solvent	μ^a	β:α ratio[b] (yield, %)[c]
1	CS_2	0	53:47 (58)
2	PhMe	0.37	82:18 (59)
3	PhMe:Cl_2C=CHCl (50:50)		76:24[d] (57)
4	**Cl_2C=CHCl**	**0.8**	**87:13 (56)**
5	Et_2O	1.15	71:29 (63)
6	Cl_2C=CHCl:CH_2Cl_2 (50:50)		82:18[d] (56)
7	CH_2Cl_2	1.6	54:46 (57)
8	THF	1.75	42:58 (81)
9	EtOAc	1.78	64:36 (64)
10	H_2C=CHCN	3.87	24:76 (59)
11	EtCN:Cl_2C=CHCl (50:50)		62:38[d] (64)
12	EtCN	4.05	14:86 (62)

[a]Dipole moment (debye). [b]Ratios determined by GC. [c]Isolated yield. [d]Ratios determined by ^{1}H NMR spectroscopy.

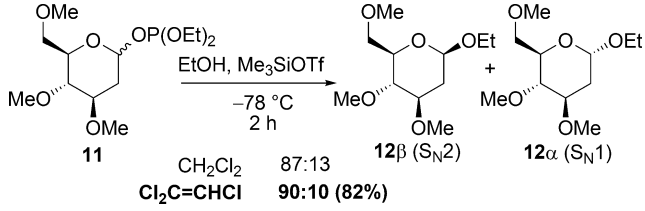
This 2-deoxyglucopyranosyl derivative was selected to study the reaction in a carbohydrate system without the influence of neighboring group participation. The biological importance of 2-deoxysugars has also been highlighted in recent literature.[57,58] These reactions proceed with similar yields regardless of the solvent system used. Whereas reactions with CH_2Cl_2 as solvent resulted in little selectivity (entry 7), nonpolar solvents such as toluene and trichloroethylene greatly favored the S_N2 product **9**β (entries 2 and 4). Reactions in polar solvents gave comparably high diastereoselectivity, but the S_N1 product **9**α was the major isomer formed from the minor equatorial oxocarbenium ion (entries 10 and 12).[22] It is not possible to rely solely on solvent polarity to predict product ratios, however, as evidenced by the use of CS_2, where no preference was observed (entry 1). Use of solvent mixtures provided no better selectivity than pure trichloroethylene (entries 3, 6, and 11). As with the acetal **4** (Table 2), increasing the reactivity of the nucleophile led to higher selectivity for the S_N2 product (Scheme 6). In this case, the use of trichloroethylene afforded the expected product **10**β with >90% diastereoselectivity, which could not be achieved with CH_2Cl_2 as solvent.

Scheme 6. Nucleophilic Substitution Reaction of Acetal 8 and Silyl Ketene Acetal 5



O-Glycosylations performed in trichloroethylene also resulted in improved stereoselectivity toward the S_N2 product. We examined the nucleophilic substitution reaction of the 2-deoxyglucopyranosyl phosphite **11** because its substitution reactions are performed under conditions similar to those reported in Tables 1−3 (Scheme 7).[59] Substitution reactions

Scheme 7. Nucleophilic Substitution of 2-Deoxyglucopyranosyl Phosphite 11 and Ethanol



using ethanol as the nucleophile in nonpolar solvents favored the S_N2 product **12**β (the β-isomer). As with the *C*-glycosylation reactions, use of the solvent trichloroethylene afforded higher selectivities than those observed with CH_2Cl_2. These experiments were performed several times to verify that the selectivity differences were significant and not the result of experimental error.

In summary, nonpolar solvents favored the S_N2 product in the *C*- and *O*-glycosylation reactions of tetrahydropyran acetals and 2-deoxyglucopyranosides, and polar solvents favored the S_N1 product. Trichloroethylene was identified as a particularly effective nonpolar solvent for the synthesis of the S_N2 product when compared to other more commonly used solvents such as dichloromethane and toluene.

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■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, product characterization, stereochemical proofs, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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