Specific features of the behavior of α- and β-glycosylfluoride tetraacetates during chemical ionization in isobutane and tetramethylsilane

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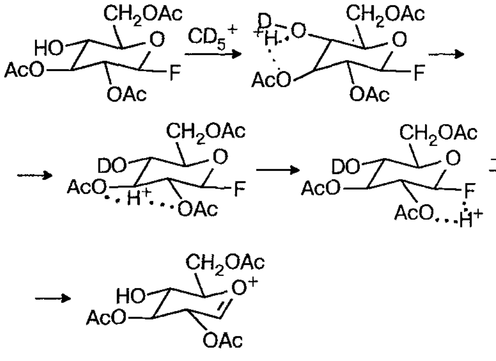
Reactions of α- and β-glycosylfluoride tetraacetates with trimethylsilicenium ion in the gas phase during chemical ionization have been studied. The $[M+SiMe_3]^+$ ions formed from the glycosylfluorides are more stable than the corresponding $[M+H]^+$ ions. The cleavage of the weakest glycosidic bond leading to the generation of glycosidic ions is not dominant for the trimethylsilylated ions, as it has been observed in the corresponding protolytic reactions. The ratio of the intensities of the $[M+SiMe_3]^+$ and $[M-F]^+$ ions characterizes the probability of the initial localization of the trimethylsilyl ion at the glycosidic center; the equatorial orientation of fluorine at C(1) makes it possible for the electrophile to bond with this substituent. Generation of the glycosidic ions is rather weakly affected by increasing temperature, whereas $[M-AcO]^+$ formation is significantly intensified.

Key words: mass-spectrometry, chemical ionization, tetramethylsilane, glycosylfluorides, anomeric effects, fragmentation, gas phase.

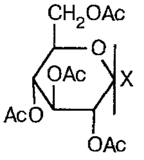
Earlier we have shown[1] that, under conditions of chemical ionization (using isobutane as a gas-reagent), the derivatives of monosugars give protonated molecular ions (PMI) whose decay involves the preferential elimination (up to 80—100 %) of the proton of the gas-reagent together with the substituent at C(1), which is caused by migration of H^+ from one functional group to another (Scheme 1).

Therefore, regardless of the place at which it is initially localized, H^+ proves to be bonded to the reactive center, i.e., to the functional group possessing the weakest bond, *viz.*, to the fluorine atom at C(1) in glycosylfluorides, which is the least nucleophilic atom among the heteroatoms of the molecule. It is this group which is eliminated together with H, as is shown in Scheme 1. The migration process is apparently accompanied by chelation. The high migration ability of nonsolvated H^+ and its inclination to chelation are caused by its small size (in the first approximation it is a point positive charge), which provides the strong interaction with neighboring functional groups.

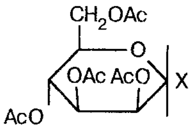
Scheme 1



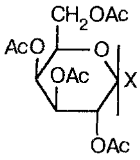
In this work the interaction between α- and β-glycosylfluorides (**1—10**) and a bulky analog of the proton, *i.e.*, the $SiMe_3^+$ ion, has been studied to reveal its ability to migrate and to chelate.



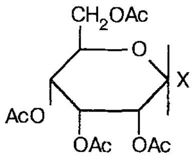
1: X = α-F
2: X = β-F



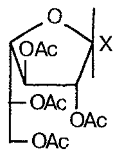
3: X = α-F
4: X = β-F



5: X = α-F
6: X = β-F



7: X = α-F
8: X = β-F



9: X = α-F
10: X = β-F

$F{-}CH_2(CH_2)_4CH_3$

11

The chemical ionization mass spectrum of 1-fluorohexane (**11**) was also studied for comparison (using $SiMe_4$ as a gas-reagent).

Experimental

Mass spectra were obtained on a Kratos-MS-30 spectrometer, the energy of ionizing electrons was 200 eV, and the

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Table 1. Characteristics of CI mass spectra (gas reagent is tetramethylsilane) of 2,3,4,6-tetra-*O*-acetyl-D-hexapyranosylfluorides and 1-fluorohexane

T/°C	$[M+SiMe_3]^+$ m/z 423	$[M-F]^+$ m/z 331	$[M-AcO]^+$ m/z 291	$[M+SiMe_3]^+$ m/z 423	$[M-F]^+$ m/z 331	$[M-AcO]^+$ m/z 291
		α-F-Gal-*p*			β-F-Gal-*p*	
100	100	15.0	27.6	100	48.0	21.0
	(0.702)*	(0.105)	(0.193)	(0.592)	(0.284)	(0.124)
200	52.0	16.0	100	40.1	24.0	100
	(0.310)	(0.095)	(0.595)	(0.244)	(0.146)	(0.610)
		α-F-Gl-*p*			β-F-Gl-*p*	
100	100	5.0	36.0	100	10.5	27.0
	(0.710)	(0.035)	(0.255)	(0.728)	(0.076)	(0.196)
200	51.0	10.2	100	100	15.0	100
	(0.317)	(0.063)	(0.620)	(0.466)	(0.069)	(0.465)
		α-F-Allo-*p*			β-F-Allo-*p*	
100	100	7.9	5.1	100	20.5	2.0
	(0.885)	(0.070)	(0.045)	(0.817)	(0.167)	(0.016)
200	100	8.8	23.5	100	17.0	19.6
	(0.756)	(0.066)	(0.178)	(0.732)	(0.124)	(0.144)
		α-F-Man-*p*			β-F-Man-*p*	
100	100	13.4	13.7	100	14.3	7.8
	(0.787)	(0.105)	(0.108)	(0.819)	(0.117)	(0.064)
200	92	22.6	100	100	15.0	68.0
	(0.429)	(0.105)	(0.466)	(0.518)	(0.078)	(0.404)
		$F-CH_2(CH_2)_4CH_3$				
	m/z 177	m/z 85				
100	0	100	—			

* Probabilities of ion formation are given in brackets

temperature of the ion source was 100 and 200 °C. Constant pressure of the gas-reagent (0.2 Torr) was maintained by an external manometer arranged in the inlet system. Tetramethylsilane from Merck of 99.7 % purity was used. Samples were injected directly. Rate constants of the decay of the $[M+H]^+$ and $[M+SiMe_3]^+$ ions were calculated according to the procedure described in Ref. 2.

Results and Discussion

The parameters of the mass spectra of glycosylfluorides **1—10** obtained at two ionization source temperatures are given in Table 1. In all of these mass spectra three main peaks are present, which correspond to the $[M+SiMe_3]^+$ (usually these peaks are of a maximal intensity), $[M-F]^+$, and $[M-AcO]^+$ ions. Unlike the corresponding PMI, the $[M+SiMe_3]^+$ ions, of the monosugars studied are more stable. In addition, the cleavage of the weakest glycoside bond to form $[M-F]^+$ ions is not the dominating process, as it is in the case of fragmentation of the corresponding PMI.

According to Table 1, the main route of the decay of $[M+SiMe_3]^+$ adducts is the generation of $[M-AcO]^+$ ions. This indicates that, in the case of the $[M+SiMe_3]^+$ ions, the weakest bond is not the only one to be preferentially broken. The direction of decay is determined by the probability of the localization of the electrophile on this or that functional group. Since there are four AcO groups for one fluorine atom in tetraacetates of glycosylfluorides, the $[M-AcO]^+$ ions are preferentially formed, and not $[M-F]^+$, i.e., the energetically less favorable processes take place.

We have shown[1] that elimination of AcOH from the MH^+ glycosylfluoride ions is less characteristic than elimination of HF.

The interaction of a polyfunctional molecule with a trimethylsilyl ion allows either thermodynamic control of the generation of $[M+SiMe_3]^+$ ions in the case of their high stability (similar equilibrium protonation in the gas phase is practically impossible), or kinetic control if the rate of heterolysis of an adduct is significantly higher than the rate of its generation.[3,4]

Thus, the general scheme for the formation and decay of $[M+SiMe_3]^+$ ions can be presented as follows (Scheme 2).

Probably, adduct **A** (Scheme 2), where the trimethylsilyl ion is localized at the fluorine atom, is unstable, which is indicated by the absence of the $[M+SiMe_3]^+$ ion peak in the CI mass spectrum of fluorohexane (Table 1) and by the low stability of the $[M+SiMe_3]^+$ adducts in the case of chlorohexylhalides.[3]* This suggests that $k_2 > k_1$. Then the rate of generation of glycoside ions **B** is determined by the rate constant k_1. The high stability of the $[M+SiMe_3]^+$ glycosylfluoride ions is presumably due to the high stability of **C** type adducts, in which the $SiMe_3^+$ ion is localized at the

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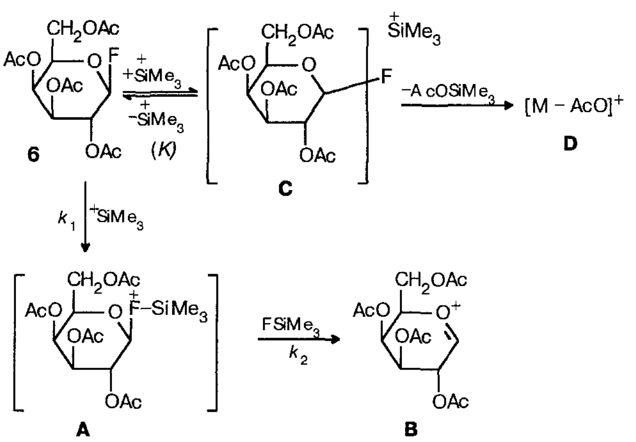
* For the same reason, analogous PMI structures are unstable, since alkylhalides do not give stable MH^+ ions.

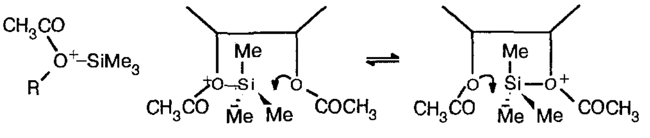
oxygen atoms of the acyloxy groups. The probability of the formation of **C** ions under the experimental conditions depends on the equilibrium constant *K* (Scheme 2).

Scheme 2



Increasing the temperature influences the rate of the generation of glycosyl ions in a relatively low extent (see Table 1), but it substantially facilitates the formation of **D** type ions, and this confirms the above-given arguments. In this case, an increasing the temperature is accompanied by fragmentation of the more stable adducts, in which the trimethylsilyl ion is localized at the acyloxy groups, and, therefore, the intensity ratio of the peaks of the fragment ions reflects the degree of the initial localization of the $SiMe_3^+$ electrophile in the molecules.

A possible explanation for these facts is as follows. The interaction of the trimethylsilyl ion and alkylacetates[5] leads to the formation of **E** type acyltrimethylsilylalkyloxonium ions. Hence, it can be proposed that, in molecules containing several acyl groups, migration of the trimethylsilyl moiety from one of them to another should be similar to intramolecular S_N2-substitution at the silicon atom $Si(F^1 \rightleftharpoons F^2)$. In order for this transformation to occur, the approach of a nucleophile from the side opposite to a leaving group is required, which involves overcoming the high entropy barrier that retards the migration.



E **F¹** **F²**

Scheme 3

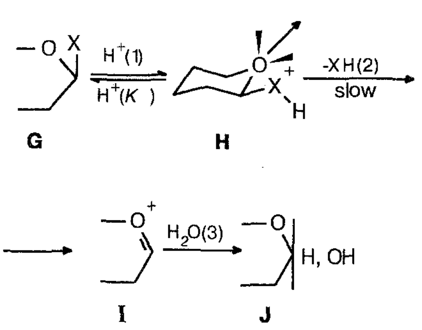


Table 2. Relative rate constants of acid hydrolysis in solution and of glycosyl ions generation under CI conditions of α- and β-hexapyranosylfluorides in an isobutane and tetramethylsilane medium

Compound	$k_{[M+SiMe]^+}$	$k_{[MH]^+}$	k^*_{sol}
α-F-Glu-*p*	1.0	1.0	1.0
β-F-Glu-*p*	6.2	6.2	1.9
α-F-Man-*p*	2.8	1.0	2.4
β-F-Man-*p*	2.9	12.8	5.7
α-F-Gal-*p*	2.8	1.9	5.2
β-F-Gal-*p*	9.0	41.5	9.2
α-F-All-*p*	1.7	1.2	—
β-F-All-*p*	7.3	42.0	—

* Relative rate constants of hydrolysis of the corresponding methylglycosides.[2]

It should be noted that an increase in temperature favors generation of glycosyl ions[1] from $[M+H]^+$ and, probably, facilitates the achievement of an equilibrium in the series of prototropic processes associated with migration of H^+ from the place of its original localization to a reactive center. Thus, the principal difference observed in the behavior of the $[M+H]^+$ and $[M+SiMe_3]^+$ ions of polyfunctional molecules is most probably caused by the difference in the reactivity of H^+ and $SiMe_3^+$. One should pay attention to the fact that, regardless of the substantial differences in the mechanisms of the formation and decay of $[M+H]^+$ and $[M+SiMe_3]^+$ monosugar ions, the rate constants of generation of glycoside ions correlate with the rate constants of hydrolysis of the corresponding monosugars in solution (Table 2). In addition, both in the gas phase and in solution, the reactivity of equatorial anomers is greater.[6]

The generally accepted mechanism for glycoside hydrolysis is given in Scheme 3.[7]

The differences in the hydrolysis rate constants of the anomers with equatorial and axial substituents at C(1) are explained by the reversed anomer effect,* which (in the case of the former anomer) increases the

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* The reversed anomeric effect is caused by the electrostatic interaction between the negative end of the resulting dipole created by the lone electron pairs of oxygen atoms of the pyranose ring and the positive charge on the equatorial substituent at C(1) (hydrogen ion in Scheme 3).

Table 3. Parameters of CI mass spectra of α- and β-galactofuranosides (relative intensities (%))

Compound	MH^+ m/z 351	$[M-F]^+$ m/z 331	$[M-AcO]^+$ m/z 291	$[M+SiMe_3]^+$ m/z 423	$[M-F]^+$ m/z 331	$[M-AcO]^+$ m/z 291
	Isobutane			Tetramethylsilane		
α-F-Gal-*f*	4.0 (0.03)	100 (0.71)	37.0 (0.26)	30.7 (0.21)	16.3 (0.11)	100 (0.68)
β-F-Gal-*f*	7.2 (0.05)	34.0 (0.24)	100 (0.71)	34.0 (0.22)	18.2 (0.12)	100 (0.66)

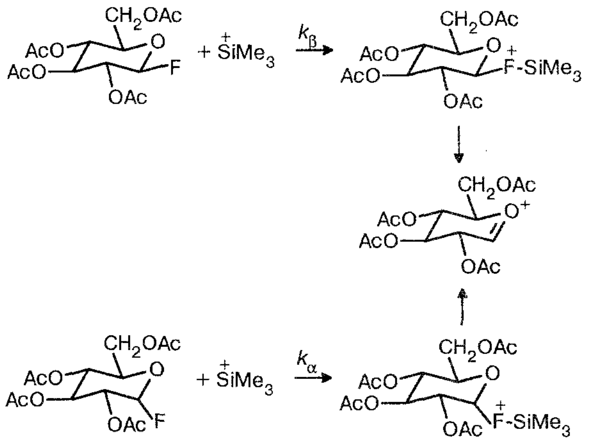
stability of the $[M+H]^+$ ions of the equatorial anomers. This effect is accompanied by an increase in the equilibrium constant K and, therefore, by an increase in the hydrolysis rate of these anomers.

Under the conditions of protonation in the gas phase, only the stage of PMI decay was investigated (analogous to the limiting stage 2 in the reaction of acid hydrolysis, Scheme 3), and, therefore, the differences in the behavior of PMI of the equatorial and axial anomers[1] testify to the fact that the ions of the former are more disposed to fragmentation. However, taking into account the instability of **H** ions in the gas phase (see above), it can be concluded that the higher reactivity of the β-anomers is caused by the higher probability of localization of a proton on their X-atom. This is presumably favored by an anomeric effect. The effect of the hindrance on the approach of H^+ towards an equatorial substituent at C(1) seems to be insignificant due to the small size of the proton. The high reactivity of the proton and its inclination to chelation should be the main factors in localization of the H^+ on aglycone. Thus, H^+ at an axial substituent at C(1) should participate in the chelation processes with other functional groups of the cycle more effectively than H^+ at an equatorial substituent due to the increase in the stability of the PMI of the axial anomers, and, therefore, due to the differences in the reactivities of the α- and β-anomers.

Using $SiMe_3^+$ as a gas-reagent for the study of anomeric pairs excludes migration and chelation of the electrophile and, therefore, simplifies the interpretation of the results. If instability of the type **A** $[M+SiMe_3]^+$ adducts is presumed, the higher reactivity of the equatorial anomers can be explained by the increased rate of interaction of the neutral β-anomer with the trimethylsilyl ion ($k_\alpha < k_\beta$, Scheme 4) due to both the anomeric effect and the greater accessibility of the equatorial substituent.

The influence of the anomeric effects on the rate of generation of glycosyl ions (Scheme 4) is apparently the same for all of the equatorial anomers, and the significant differences in the rate constants for the anomers studied (Table 2) are mainly caused by steric hindrances during the approach of $SiMe_3^+$ to substituents at C(1). It can be seen from the conformational formulas that, in the case of the α-anomers, the approach to a fluorine atom is most favorable for the *manno-* and *galacto-*isomers (possessing two AcO substituents in the *trans*-position, while in the *manno*-isomer the nearest substituent at C(2) is also in the *trans*-axial position). These isomers generate glycosyl ions more actively than the other isomers. Axial anomers of the *gluco-* and *allo-*isomers have two and three AcO-substituents, respectively, in the *cis*-position relative to a substituent at C(1), and the rate of the generation of glycosyl ions for these compounds is lower.

Scheme 4



In the case of the β-anomers, the approach to a substituent at C(1) in mannoside is the most complicated (the substituent at C(2) is in the *cis*-axial position), and it is this β-anomer which has the minimal rate constant. The equatorial β-anomers of the *gluco-*, *galacto-*, and *allo*-isomers decompose with approximately equal rates and, therefore, it is difficult to correlate these rates with steric effects.

The great differences in the rate constants of glycosyl- and allosylfluorides are caused by the rather favorable conditions for the approach of $SiMe_3^+$ ions to the equatorial substituent at C(1) (the lowest number of AcO-substituents in the ring in the *cis*-position is in the β-anomers). These differences are less significant for galactosylfluorides, presumably due to relatively weak interaction with the equatorial fluorine atom (two AcO substituents in the *cis*-position to F). The practically equal rate constants for α- and β-mannosylfluorides attest to the fact that, when $SiMe_3^+$ approaches F, steric hindrance is significant for the β-anomer (the axial substituent at C(2) greatly retards the process, which leads to a significant decrease in k_β), while it is minimal in the α-anomer (the axial substituent at C(2) practically does not retard the process, which causes an increases in k_α).

The distinctive features in the behavior of the $[M+H]^+$ and $[M+SiMe_3]^+$ ions can be illustrated using the example of the α- and β-anomers of furanosylfluorides **9—10**. It was shown[8] that a change in the configuration of the carbon atoms in the cycle of furanosylfluoride acetates can be favorable for the creation of «traps» for H^+ ions (due to drawing together of the functional groups), which inhibit H^+ migration and determine the character of PMI destruction. It is clear from Table 3 that formation of the $[MH-HF]^+$ ion is the most characteristic for α-furanosylfluoride **9**, while, in the case of β-furanosylfluoride **10**, the $[MH-AcOH]^+$ ion preferentially forms. The $SiMe_4$-CI mass spectra of α- and β-galactosylfluorides are practically identical (only an insignificant decrease in the stability of adduct ions of β-anomer **10** as compared to that of α-anomer **9** is observed), which attests to the inability of the trimethylsilyl ion to either migrate, or to chelate. The fragmentation of the adducts of $[M+SiMe_3]^+$ characterizes the degree of initial localization of $SiMe_3^+$ in a polyfunctional molecule.

Thus, the differences in the reactivities of the α- and β-anomers under conditions of acid hydrolysis are explained by the anomeric effect, which favors localization of H^+ at an equatorial substituent at C(1). In the gas phase, the analogous differences are also caused by probable localization of the electrophile at aglycone. In the case of the trimethylsilyl ion, this probability is determined by the anomeric effect and by steric hindrance to the approach of the $SiMe_3^+$ ion to a substituent at C(1), while for the proton it is determined by the anomeric effect, by the migration ability of H^+, and by its disposition to form chelates.

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