Substituent Dependence of the Diastereofacial Selectivity in Iodination and Bromination of Glycals and Related Cyclic Enol Ethers

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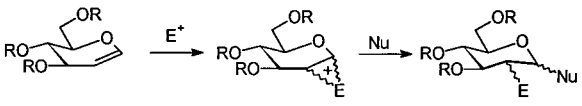
The stereochemical course of the electrophilic iodination and bromination of tri-*O*-benzyl-D-glucal under various conditions has been compared to that of substituted dihydropyrans **2**−**5**. IN_3 addition in acetonitrile affords *trans*-α-iodoazides (80−87%), besides small amounts of *trans*-*β*-adducts, in the presence or the absence of benzyloxy substituents at C-3 or C-4, and in agreement with bridged iodonium ion intermediates. In contrast, the diastereofacial selectivity of bromine addition in dichloroethane going through open bromo oxocarbenium ions depends strongly on the substituents. Whereas the *trans*-α-dibromides are the main (85−95%) adducts in the absence of C-4 and C-5 substituents, in their presence a moderate to exclusive selectivity for cis-α-addition (60−99%) is observed. The predominance of trans-α-addition is again observed whatever the substituents when the bromination is carried out in the same solvent but with a tribromide ion salt, supporting a concerted addition of the two bromine atoms under these conditions. Finally, bromine addition in methanol exhibits a completely different behavior with the nonselective formation of *trans*-α- and *trans*-*β*-methoxybromides and a small dependence on the substituents. In agreement with the absence of azide trapping of any cationic intermediate, it is concluded that these brominations which do not go through an ionic intermediate are concerted additions of bromine and methanol with very loose rate- and product-determining transition states. Finally, the substituent conformation at C-4 influences drastically the stereoselectivity in all these brominations. Evidence for α-anomeric control of the nucleophile approach at C-1 is given by the highly predominant formation of α-adducts, except in the methanolic bromination. The factors determining the versatile selectivity of the electrophile approach are discussed in terms of PPFMO theory and of the special mechanisms of glycal reactions.

Introduction

For many natural products, a selective link-up between an aglycon and a carbohydrate is the ultimate requirement for a total synthesis. Among the different methods reported[1] to obtain stereocontrolled constructions of glycoside bonds one of the more fruitful approach consists of the use of glycals.[2] These compounds can indeed be easily activated by addition of an electrophile which, through the formation of an onium species (eq 1), makes the addition of the suitable nucleophile at the anomeric position possible.



(1)

In this synthesis strategy, in agreement with all the other modern synthetic procedures, the central problem is the possibility to predict and to control the diastereofacial selectivity.[3] It has been reported[4] that in the case of glycals the below-plane approach of the electrophile is generally preferred, with the exception of above-plane attack of iodine[2] and selenium.[5] However, a thorough search in the literature for glycal additions revealed that for each electrophile the face selectivity depends highly on glycal substitution and reaction conditions, and various interpretations have been proposed to rationalize the observed behavior.

For example, the electrophilic addition of halogens to cyclic enol ethers has been investigated early by Lemieux and Fraser-Reid[6] who proposed a general mechanism involving the initial formation of carbenium ions which, upon nucleophilic attack by halide ion, give mainly the products of thermodynamic control. Later on, it has been shown that the product formation is under kinetic control and that the stereoselectivity depends on the solvent polarity,[7−9] the structure of the enol ether, and the nature

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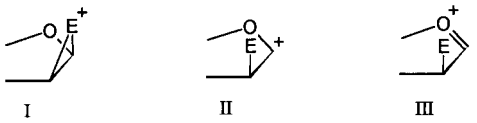
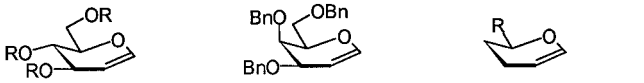
of the halogen.[9] In particular, in the bromination reactions a dependence of the product distribution on the electron-donating or withdrawing effect of the substituent at C-6 has been found and these results have been interpreted[9] in terms of the effect that the 6-substituent may exert on the nonbonding electron pair of the ring oxygen atom, affecting the charge distribution in the intermediate whose predominant structure can be either I, II, or III.



I II III

More recently, a stereoelectronic α-anomeric effect[10] able to stabilize the transition states related either to the electrophilic step or to the nucleophilic step has been invoked[11] to rationalize the product distribution obtained in the additions of halogens to tri-*O*-benzyl-D-glucal. Finally, polarized π-frontier molecular orbital theory (PPFMO) in which the reagents and not the transition states are taken into account, has been applied[12] recently for interpreting the stereochemical behavior of several dihydrofurans and dihydropyrans observed both in protonation and sulfenylation, two reactions considered as models of additions via open and bridged intermediates, respectively. Also of interest in electrophilic additions to glycals are the recent data[13] and calculations[14] on the stereochemistry of the nucleophilic trapping of six-membered-ring oxocarbenium ions showing the pseudo-axial preference of these ions bearing benzyloxy substituents.

In this paper, the stereochemical course of the electrophilic additions of halogens, and in particular of bromine, to tri-*O*-benzyl-D-glucal (**1**) is compared with that of the dihydropyrans **2**−**5**, to obtain further information about the factors which contribute to the stereofacial selectivity in the electrophilic addition to cyclic enol ethers.



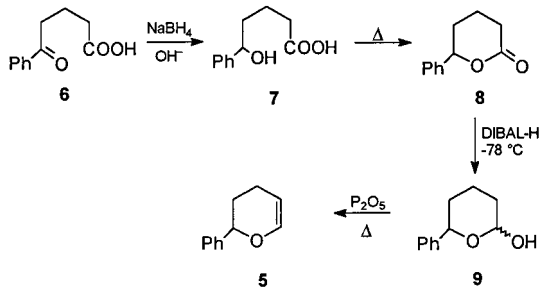
1: R = Bn
2: R = Ac

3

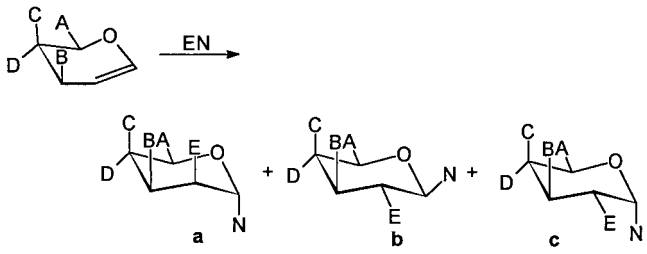
4: R = CH_2OBn
5: R = Ph

These substrates were chosen for the following reasons. First, compounds **1**−**4** were studied theoretically applying the PPFMO method and experimentally in protonation and sulfenylation. Second, they are suitable substrates to give indications about the contribution to the stereoselectivity of some specific factors, such as the stereoelectronic α-anomeric effect, the polarization of the π-orbitals, the effect due to the axial substituent at C-4 and their dependence on the bridging in the ionic intermediates. While the nucleophile attack is mainly determined by stereoelectronic α-anomeric effect whatever the substituents, it is shown that the kinetically controlled stereochemistry of the electrophile approach depends significantly on the substituents and on the reaction mechanism.

Scheme 1



Scheme 2



Results

1. Synthesis of Dihydropyrans 4 and 5. 3,4-Dihydro-2-benzyloxymethyl-2*H*-pyran (**4**) was obtained from commercial 3,4-dihydro-2-hydroxymethyl-2*H*-pyran by benzylation. 3,4-Dihydro-2-phenyl-2*H*-pyran (**5**) was prepared according to the sequence of reactions reported in Scheme 1.

Treatment of 4-benzoylbutyric acid (**6**) with $NaBH_4$ afforded the corresponding alcohol **7**, which has been warmed, in the absence of solvent for 2 h, at 80−106 °C under vacuum using a Dean−Stark trap to remove the formed H_2O. Reduction of **8** with DIBAL-H at −78 °C afforded the diasteroisomeric mixture of lactols **9** that may be converted by dehydration with P_2O_5 in toluene to dihydropyran **5**.

2. Product Analysis. The halogen additions (IN_3, Br_2, and Br_3^-) to compounds **2**−**5** were performed in the dark at 0 and/or 25 °C. The products have been extracted from the mixtures immediately after the end of the reactions. The composition of the mixtures was determined by NMR spectroscopy. The structures of the resulting products, reported in Scheme 2, were established on the basis of their ^1H and ^{13}C NMR spectra, by comparison with previously reported data (gluco, manno, galacto and talo derivatives) or from a combination of the following factors: (i) the $J_{1,2}$ coupling constants, (ii) the chemical shifts of H-1, (iii) the chemical shifts of C-1, and (iv) the $J_{2,3}$ coupling constants.

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(10) The stereoelectronic α-anomeric efect has been shown to occur as a general effect in X−A−Y segments. It is described in terms of endo- and exo-anomeric effects. The endo-effect is related to the preference of an electronegative group at the anomeric carbon for the axial orientation. The preference is due partly to inductive effects (dipole−dipole interactions between the endo-cyclic oxygen lone pairs and those of the electronegative substituent, X), partly to the stabilizing overlap of the $n_x \rightarrow \sigma^*_{c-x}$ orbitals. See: Kirby, A. J. *Stereoelectronic Effects*; Oxford Science Publications: New York, 1996.
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Table 1. Product Distribution in Electrophilic Additions to Compounds 1−5

		products					
		a		**b**		**c**	
	reagents	N, E	%	N, E	%	N, E	%
1	ICl/NaN_3/-CH_3CN[a]	N_3, I	87	N_3, I	13		
4			80		20		
5			84		16		
1	Br_2/DCE[b]	Br, Br	40			Br, Br	60
2			20				80
3			<1				>99
4			95				5
5			86				14
1	Bu_4NBr_3/DCE[b]	Br, Br	87	Br, Br	traces	Br, Br	13
2			93				7
3			43				57
4[c]			95				5
5[c]			90				10
1	Br_2/MeOH[b]	MeO, Br	55	MeO, Br	45		
2			70		30		
3			30		70		
4			56		44		
5			62		38		

[a] 0 °C. [b] 25 °C. [c] 20−25% unidentified products.

The product distributions observed for all compounds **2**−**5** are reported in Table 1, which also shows the distribution data related to glycal **1**. The NMR data of all the addition products are given in Table S1.

3. Stereochemistry. In the IN_3 addition (generated in situ from NaN_3 and ICl) to compounds **4** and **5**, the main products are the α-*trans*-azide-incorporated adducts,[15] **a** (N, E = N_3, I). The ratio between the α-trans adducts and the *β*-trans, **b** (N, E = N_3, I), is practically the same as that observed in the reaction of **1**, showing that the presence of the substituents at C-3 and C-4 does not affect significantly the product distribution for this addition.

Bromine addition in 1,2-dichloroethane (DCE) gives always two products: the α-trans, **a** (N, E = Br, Br), and the α-cis adduct, **c** (N, E = Br, Br). However, the ratio is markedly affected by the nature and position of the substituents at C-3 and C-4. The cyclic enol ethers **4** and **5** lead to the preferential formation of the adduct **a**, while all the other substrates give selectively or exclusively the corresponding dibromides **c**. Moreover, this selectivity depends on the nature of the substituents (compare **1** and **2**) and on their orientation on the pyran ring (compare **1** and **3**). When bromine addition is carried out in methanol the *trans*-methoxy adducts, the α-trans, **a** (N, E = OCH_3, Br) and the *β*-trans, **b** (N, E = OCH_3, Br), were formed as the sole products. These compounds are obtained in a ratio close to unity from **1**, **4** and **5**, indicating that in this solvent the product stereochemistry does not depend significantly on the substituents at C-4 and C-5. In contrast, the stereochemistry at C-4 seems to affect markedly the reaction.

Finally, the electrophilic addition of bromine using a tribromide salt proceeds, with the exception of the galactal derivative **3**, stereoselectively leading preferentially to the α-trans adduct, **a** (N, E = Br, Br). Nevertheless, in the case of enol ethers **4** and **5** the reaction was characterized by the formation of a mixture (20−25%) of unidentified products.

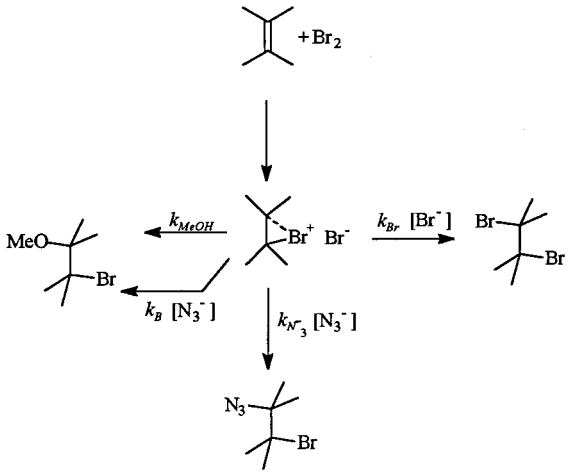
(15) α-trans (*β*-cis) adducts: α(or *β*) stands for the nucleophile entering in the α- (or *β*-) anomeric position, i.e., for an axial (or equatorial) or below-face (or top-face) nucleophilic attack. "trans" (or "cis") is related to the relative orientation of the electrophile, E, and the nucleophile, N.

Table 2. Product Ratios Observed for Bromination of 2 in MeOH in the Presence of N_3^-, at 25 °C

	product ratio		k_{N3}/k_{MeOH}[a]	
$[NaN_3]$	Br, N_3	Br, OCH_3	(M^{-1})	$(k_{N3} + k_B)/k_{N3}$[a]
0.15	5.6	94.4		
0.2	10.6	89.4		
0.27	13.8	86.2		
			0.595	1.006

[a] Reference 19.

Scheme 3



4. Bromine Addition in Methanol in the Presence of NaN_3. The addition of Br_2 in methanol in the presence of a large excess of NaN_3, which generated in situ BrN_3,[16,17] generally afforded the same product distribution as that observed in the absence of the added salt. The bromomethoxy derivatives **a** and **b** were indeed the sole products observed in the crude reaction mixtures arising from the addition to **1**, **3**, **4** and **5**. In other words, at variance with previous results on bromination of acyclic alkenes,[17] there is no trapping of any cationic intermediate by the strongly nucleophilic azide ion.[18]

Only in the case of **2**, a detectable amount of bromoazide adducts, which increases with $[N_3^-]$ is observed (Table 2).

The product data of Table 2 fit fairly well the usual equation[17,18] (eq 2), based on Scheme 3 in which the reaction products are assumed to arise from the nucleophile trapping of an intermediate.

$$\frac{1}{f_{az}} = \left(1 + \frac{k_B}{k_{N_3}}\right) + \frac{k_{MeOH} + k_{Br}[Br^-]}{k_{N_3}} \frac{1}{[N_3^-]} \qquad (2)$$

In this equation, f_{az} is the fraction of bromoazide in the total product mixture, k_B, the rate constant of the azide-catalyzed trapping of the intermediate by methanol, k_{N_3}, the rate constant for the diffusion-controlled azide trapping[17,18] of this intermediate (in methanol, k_{N_3}

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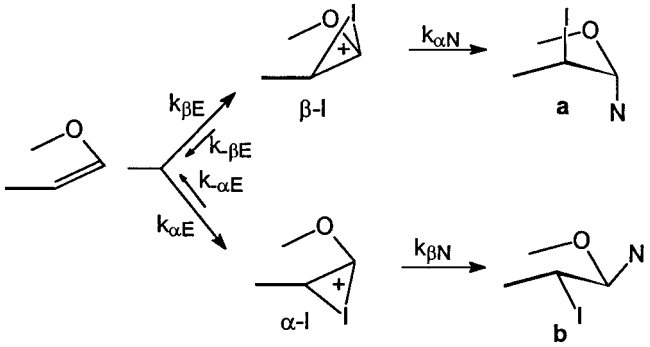
$= 10^{10}$ M^{-1} s^{-1}) and k_{MeOH} and k_{Br^-}, the rate constants for the reaction of the cationic intermediate with methanol and bromide ions. (In the present case, the term $k_{Br^-}[Br^-]$ can be neglected since no dibromide is obtained.) The fit of the product data to eq 2 provides[19] the kinetic data shown in Table 2 with $k_{MeOH} = 7 \times 10^9$ M^{-1} s^{-1}. In other terms, the lifetime in methanol of the intermediate issued from the bromination of **2** is 6×10^{-9} s. Furthermore, this reaction is not azide-catalyzed since k_B is negligible (Table 2).

Discussion

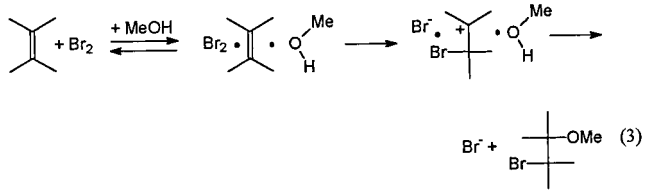
The present interest[3] in understanding and predicting diastereofacial selectivity is not surprising considering the ubiquity of glycal reactions in synthetic organic chemistry. Despite much work, however, most of the assumptions on the interactions contributing to the small activation energy differences leading to the observed selectivities are still controversial. In particular, as regards electrophilic additions to cyclic enol ethers (glycals) under kinetic control, apart from steric effects, a number of factors, which can be classified as stereoelectronic, conformational, inductive and electrostatic, have been alternatively invoked[7−11] to account for the observed stereochemistry, while the PPFMO method has been proposed[12] to predict the selectivities. Upon accounting for the expected differences in the mechanisms of the investigated reactions, protonation implying electrophilic attack at C-2 and sulfenylation both at C-1 and C-2, this method has been suggested to be able to predict generally the stereoselectivity of the electrophilic additions to glycals since "it does not focus upon a single electronic interaction of the dissymmetric σ framework as being responsible for the selectivity. Rather, it accounts for all electronic effects as part of a molecular orbital treatment".[12] It is noteworthy that although this method predicts an equatorial selectivity both for gluco and galacto derivatives, as well as for **4**, in reactions involving electrophilic attack at both C-1 and C-2 to form a bridged intermediate (sulfenylation), an axial selectivity in the case of **4** and again equatorial for glucals and galactals has been forecast when, as in deuteration, the reaction implies the initial electrophilic attack at C-2.

It must be considered that, with the term "electrophilic addition", is regarded a large class of organic reactions whose essential feature is that the alkene reacts with a reagent in a such way that the transition state, or the intermediate, has a cationic character. Electrophilic addition can occur in a sole step, characterized by the concerted attacks of the electrophile and nucleophile, at both ethylenic carbon atoms without formation of an intermediate with a significant lifetime in the presence of nucleophiles. Alternatively, the electrophilic addition can be a two step process involving the formation of an ionic intermediate with a sufficient lifetime to diffuse through the solvent before it reacts with the present nucleophiles. Between these two limiting mechanisms when an unstable intermediate can be formed with a very short but significant lifetime, a preassociation stepwise

Scheme 4



mechanism[20] involving ionization within a ternary complex between the electrophile (eq 3), the ethylenic substrate and the nucleophile has been shown to occur in electrophilic bromination.[21] In this latter mechanism, the stereochemical outcome of the addition is controlled by the stereochemistry of the initially formed ternary complex.



(3)

Therefore, taking into account the generally accepted mechanisms for each of the investigated reaction and the different effects which may affect the facial stereoselectivity, the observed stereochemical behaviors can be rationalized as reported below.

i. IN_3 Addition in Acetonitrile. IN_3 addition, as sulfenylation and bromination in aprotic solvents, is a stepwise reaction involving an ionic intermediate.[22] In most cases, the formation of an iodonium ion of type I by iodination is reversible.[22] However, when its trapping agent is the strongly nucleophilic azide ion instead of less nucleophilic species such as methanol or iodide ion, the second step is likely very fast since N_3^- is known to react with carbocations at diffusion-controlled rates.[18] Therefore, return (Scheme 4) is not very significant in the case of IN_3 addition, so that the product distribution shown in Table 1 is close to be kinetically controlled. The insignificant return is supported by the fact that iodoalkoxylation[24a] of the same glucals by iodine addition in protic solvents exhibits a stereoselectivity smaller than that shown in Table 1 for azidoiodination. In agreement with the complete iodine bridging of the intermediate, the addition of the two electrophilic and nucleophilic partners of IN_3 is trans, whatever the substituents. The product data of Table 1 establish clearly that the C-3 and C-4 substituents do not influence markedly the stereoselectivity. Moreover, the stereochemistry of the sub-

(19) According to eq 2, the plot of $1/f_{az}$ versus $1/[N_3^-]$ gives a straight line,[17,18] the slope of which is k_{MeOH}/k_{N_3} since $[Br^-]$ is negligible as compared to $[N_3^-]$ and MeOH (no dibromide is observed). The intercept affords k_B.

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stituent at C-4 does not influence it either, since, according to previous results,[24b] azidoiodination of **1** and **3** exhibits the same stereochemical behavior.

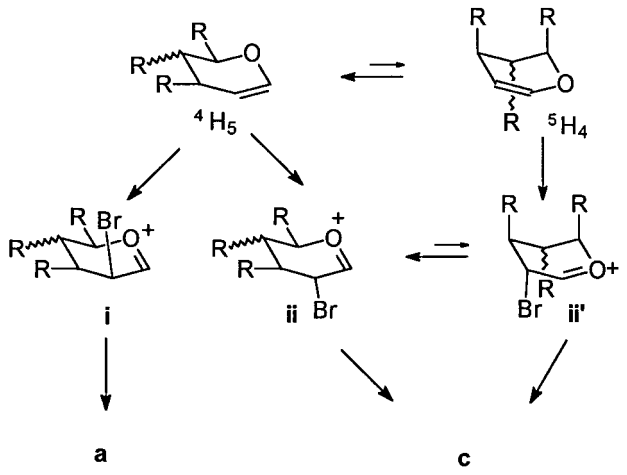
In the absence of significant return, the marked predominance of the α-*trans*-azido iodo adducts **a** is to be related to a preferred top-side axial approach of the electrophilic iodine atom to the double bond of **1**, **4** and **5**, i.e., on the face opposite to that observed and predicted by PPFMO theory for sulfenylation. The large difference between the steric requirements of the electrophilic sulfur and iodine species are probably at the origin of this disagreement. In contrast, our results are more consistent with previous results showing the iodine preference for an above-plane attack.[24]

ii. Bromine Addition in the Aprotic Dichloroethane. Bromination in DCE is also a two-step reaction involving an ionic intermediate which, according to previous results on acyclic enol ethers, is a bromo oxocarbenium ion (III).[25] Therefore, the formation of this intermediate is irreversible and the stereochemistries of the two consecutive steps are not necessarily related each other. In agreement with the unbridged nature of the intermediate, both cis and trans adducts **a** and **c** are observed, in contrast with iodination. Analogous behavior was previously found[9] in the bromination of acetyl glycals in various aprotic solvents.

A striking result is that the capture of the bromo oxocarbenium ions occurs always by nucleophilic α-attack, whatever the number and the nature of the substituents of the six-membered ring. This is not readily understood in terms of the recently established preference of these cations to react via their pseudoaxial conformation.[13] In particular, benzyloxy substituents at C-3 or C-4 were found to favor strongly this conformation because of stabilizing electrostatic interactions between the partially negatively charged hydroxyl oxygen and the cationic oxygen atom.[14] Nevertheless, the combination of steric and polar effects of the three substituents in **1**, **2**, and **3** and the differences in the requirements of the involved nucleophiles make any stereochemical interpretation hazardous.

More interestingly, the diastereofacial selectivity of the electrophilic attack of the carbon−carbon double bond is strongly substituent-dependent. In the bromination of **4** and **5**, i.e., in the absence of C-3 and C-4 substituents, the top-side axial bromine approach is largely predominant, as it was found for iodination of the same substrates and in agreement with PPFMO theory predictions when an unbridged intermediate is involved.[12] In contrast, the equatorial approach is moderately to exclusively favored when benzyloxy or acetoxy substituents are at C-3 or C-4 positions. A large preference for this approach is observed for **3** in which steric 1,3-interactions, opposing the effect of through-space electron-donation of the axially oriented electronegative substituent at C-4, play a role in determining the facial selectivity of the electrophilic step. The increased diastereoselectivity in favor of the gluco or galacto derivative **c**, on going from **1** to **2** and **3** can be rationalized considering that glycals are conformationally flexible[23] and therefore both the normal half-chair $^4H_5$ conformation and conformationally inverted isomer, $^5H_4$, may contribute to the product distribution.[23,24] Furthermore,

Scheme 5



it has been shown that the $^5H_4$ conformation becomes increasingly important for D-glucal derivatives when the C(5) substituent becomes more electronegative. Although glucal **2** exists preferentially in $^4H_5$ conformation, it is however possible that this compound reacts, at least partly, in the $^5H_4$ conformation, which is characterized by a different face diastereoselectivity with respect to $^4H_5$. In particular, the two faces of the $^5H_4$ conformation are differentiated to much extent by steric and electrostatic factors. The upper face (β) is hindered by two axial substituents, while the bottom (α) is shielded only by the axial C(4)−OR group in glucals **1** and **2**. Moreover, when the latter substituent is an acyloxy group, as in **2**, the transition state leading to the ionic intermediate **ii′** (Scheme 5) could be stabilized by a charge-dipole interaction. The bromine addition to compounds **1**−**5** is almost certainly slow compared to $^4H_5 \Leftrightarrow {}^5H_4$ interconversion. Therefore, in agreement with the Curtin-Hammett principle, the product distribution is determined exclusively by the relative energies of the competing transition states and is independent of the distribution of ground state conformers. On this basis, assuming that the transition state for Br_2 addition is half-chairlike, glycals that preferentially adopt the $^5H_4$ conformation in the transition state, as well as probably **2** and **3**, should exhibit higher diastereofacial selectivity in favor of the dibromo adduct **c**. A similar interpretation has been recently proposed to rationalize the facial stereoselectivity observed in sulfenylation of glycals bearing electronegative substituents at C-6 and polar substituents at C-4.[26]

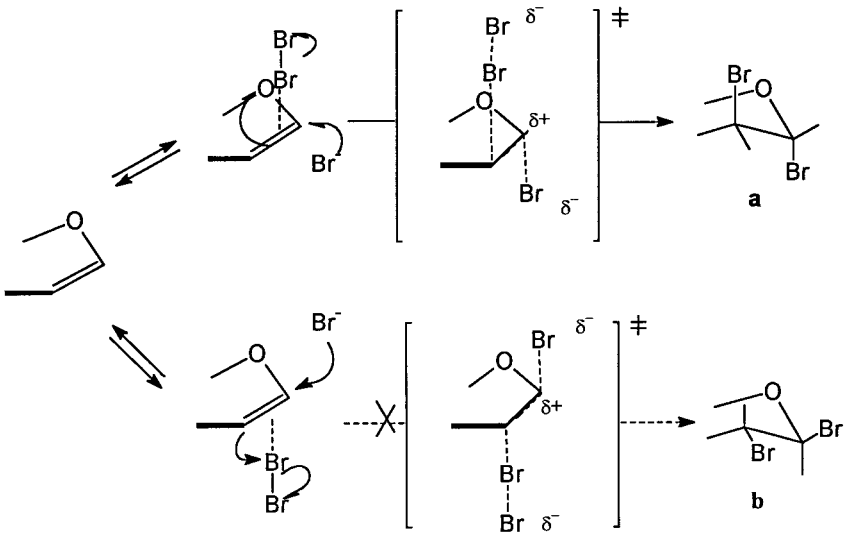
iii. Bromination Using the Tribromide Salt, Bu_4NBr_3. In contrast with bromination by free bromine, the very major product of the tribromide ion addition is the trans adduct **a** arising from the diaxial attack of the two bromine atoms, except in the case of **3**. This result agrees fairly well with the well-established mechanism of bromination by tribromide salts.[27] The trans-addition of the two bromine atoms occurs via a concerted process, i.e., without the involment of any ionic intermediate, by rate- and product-determining nucleophilic attack of a bromide ion on initially formed olefin-bromine π-complexes (Scheme 6). The stereochemical results which, again, are not predictable from the PPFMO theory, are

(25) Ruasse, M. F.; Dubois, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 3220. Ruasse, M. F. *Isr. J. Chem.* **1985**, *26*, 414.

(26) Roush, W. R.; Sebesta, D. P.; Bennett, C. E. *Tetrahedron* **1997**, *53*, 8825.

(27) Bellucci, G.; Chiappe, C.; Lo Moro, G. *J. Org. Chem.* **1997**, *62*, 3176.

Scheme 6



readily rationalized considering that the formation of α-trans adducts **a** is markedly favored by stereoelectronic α-anomeric effects. The much smaller selectivity observed for this addition to **3** may be attributed to unfavorable steric and electrostatic interactions between the axial C-4 benzyloxy group and the electrophile, which slow markedly the C(2)−Br bond formation in the axial position.

Unexpectedly, the minor products in these Br_3^--additions are not the trans adducts **b** arising from β-anomeric attack of Br^- but those resulting from a cis-addition of the two bromine atoms from the bottom face. Clearly, the unfavorable β-anomeric effect inhibits totally the trans-addition leading to **b**. The formation of the cis-addition products **c** could be attributed to the addition of some free bromine since adducts **c** are also obtained in the reaction of this electrophile (vide supra). Some free bromine arising from a preliminary dissociation of the tribromide ion according to eq 4 can, actually, be present since tribromide addition to glycals can be slow as compared to its dissociation[28] ($k_+ = 5 \times 10^2$ s^{-1} in DCE), which is not generally observed in the

$$Br_3^- \underset{k_-}{\overset{k_+}{\rightleftharpoons}} Br_2 + Br^- \qquad (4)$$

Br_3^--bromination of acyclic alkenes.

iv. Bromination in Methanol. The stereochemical outcome of bromine addition in methanol is markedly different from that of the reaction of the same electrophile in the nonprotic dichloroethane, although identical bromo oxocarbenium ion intermediates could be postulated a priori. Still more surprising is the exclusively *trans*-addition of the two electrophilic and nucleophilic partners, as it was observed for iodination via a bridged iodonium ion but not for the concerted Br_3^--bromination. Moreover, in contrast with iodination, the methanolic bromination of **1**, **4** and **5** are almost nonselective, the two adducts **a** and **b** being obtained in closely similar amounts. Only in the case of **2** or **3**, some diastereofacial selectivity is observed. This poor selectivity and its small sensitivity to substituent effects is consistent with very early and weakly charged transition states, as it was found previously for bromination of acyclic enol ethers in protic solvents.[25] The most important result for the interpretation of these data is the absence of any azide incorporation in the trapping experiments in the presence of azide ions, which suggests strongly that there is no intermediate in the methanolic bromination of these substrates, i.e., that these reactions are concerted and not stepwise (Scheme 7). This result agrees fairly well with previous findings that nucleophilic substitutions, a class of carbocation-forming reactions exhibiting some common features with bromination,[21] on glycosyl derivatives cannot involve carbocationic intermediates in the presence of strong nucleophiles.[29] For example, rate constants of 10^{12} s^{-1}and 10^{19} s^{-1}, much larger than that expected for diffusion control, has been extrapolated for the reaction of the glycosyl cation with water and azide ion, respectively, showing that this cation cannot exist when strong nucleophiles are present. Because of the destabilizing effect of the electron-withdrawing hydroxyl substituents, probably reinforced by the β-bromo substituent in bromination, these ionic species are too unstable, too short-lived to exist in the presence of strong nucleophiles and in particular in methanol. In contrast, they can exist in DCE in which the only nucleophile is the bromide ion liberated by the formation of the intermediate.

The marked differences in the diastereofacial selectivities of the tribromide ion addition and the methanolic bromination which both are concerted reactions, can be rationalized in terms of tight and loose transition states, respectively (Schemes 6 and 7). Very early transition states for bromination in methanol are supported by unusually small solvent and substituent kinetic effects on the very fast reaction of enol ethers[25] whereas tribromide ion additions involve likely late transition states with significant charge development. Therefore, the steric and electronic interactions[30] contributing to the stereoselectivity of the two reactions are markedly stronger when the nucleophile is a bromide ion.

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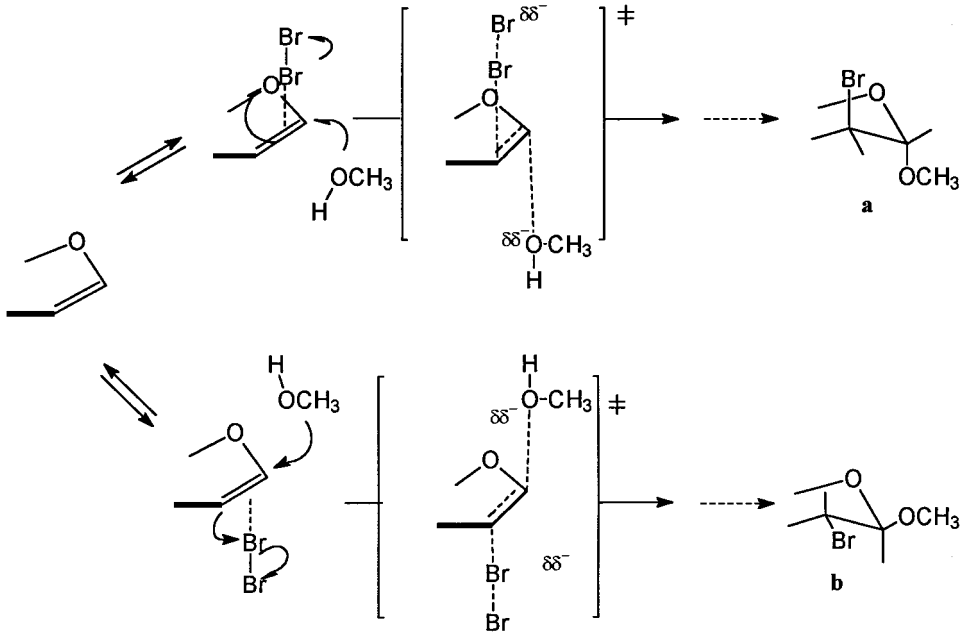
Scheme 7



In this context, the significant lifetime of the oxocarbenium ion derived from **2** ($k_{MeOH} = 3 \times 10^7$ s^{-1}) in which the substituents are acetoxy, instead of benzyloxy groups, deserves a peculiar attention. First, although the electron withdrawing effects of these two substituents are very close,[31] the trapping of the corresponding intermediate is drastically slown down. Second, a significant diastereofacial selectivity, analogous to that observed for iodination or tribromide ion addition, is restored, with a predominance of top-side axial approach of the bromine to the ethylenic bond. These two results suggest a preassociation mechanism (eq 2) for the reaction of **2** in which methanol on one side and bromine on the other side preassociate with the enolic double bond before ionization within the ternary complex in a cationic intermediate formed in sandwich between the leaving bromide and the entering methanol.[21]

Concluding Remarks

Several conclusions emerge from our stereochemical results which correspond to a kinetically controlled product formation, either since the ionic intermediate is obtained irreversibly (bromination in DCE) or quasi-irreversibly (IN_3 iodination) or since the electrophilic addition is concerted (tribromide ion reaction, bromination in methanol).

(i) Whatever the six-membered ring substituents, the favored mode of addition of the nucleophilic partner N of an electrophilic reagent EN is a below-plane approach, i.e., the stereoelectronic α-anomeric effect controls predominantly the widely preferred formation of adducts **a** and **c**. The only exception to this rule is for the reaction of bromine in methanol which does not exhibit any marked selectivity for α- or *β*-attack.

(ii) In contrast, the diastereofacial selectivity of the electrophile approach is more versatile and depends significantly on the substituents. The substituents at C-3 and C-4 influence markedly the selectivity since in their absence the electrophile approach is almost exclusively axially top-side for the reactions of **4** and **5**, except again for bromination in methanol. The axial or equatorial conformation of the substituent at C-4 plays also an important role. On going from **1** to **3** with an equatorial or axial benzyloxy substituent, respectively, the preference for the axial approach of the electrophile is strongly attenuated (Br_3^--addition, methanolic bromination) or disappears (bromination in DCE) at the benefit of an equatorial approach, in agreement with strong steric and electrostatic 1,3-interactions. Finally, the substitution of a benzyloxy by an acetoxy group has also a noticeable effect on the stereochemistry of the bromine addition in the polar and apolar solvents.

(iii) The usual interpretation in terms of the stereoelectronic preference for α-anomeric attack[10,11] still holds in most of the investigated reactions. However, a more detailed interpretation of the product-determining nucleophilic steps in terms of the preferred pseudoaxial conformation of the C-3 and C-4 benzyloxy substituents of oxocarbenium ions[13] does not fit the results quite well, probably because of the presence at C-2 of a large, polarizable halogen atom.

(iv) Finally, in regard to the electrophile approach, the PPFMO theory, which takes into account the orbital interactions in the glycal itself,[12] does not predict consistently the top-face or below-face attacks of the iodine and bromine observed in this work. This theory has been developed for models of additions via open or bridged intermediates, electrophilic protonation and sulfenylation, respectively, and could be a priori extrapolated to bromination via oxocarbenium ions and iodination via iodonium ions. Nevertheless, it is well-known that iodination and sulfenylation exhibit very different stereochemical behaviors. It is also quite obvious that bromine and proton are very different electrophiles not only in their electronic and steric requirements but also in the mechanism of their reactions.

(v) In this respect, the most important result is probably to point out that the selectivities of these reactions are closely related to their specific mechanisms. The three bromination methods used in this work involve

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all usual brominating agents but the reaction mechanisms and, therefore, the stereochemistries are very different. The addition of free bromine in an aprotic solvent is a two-step reaction involving bromo oxocarbenium ions and not bromonium ions so that the stereochemistries of the two consecutive electrophilic and nucleophilic steps can be determined by different factors. The reaction of tribromide ions is a concerted addition of the electrophile and the nucleophile, implying an enforced cooperation between the stereochemistries of the two partners. Finally, bromination of the same substrates in nucleophilic methanol appears to be also a concerted addition, even though the same reaction in the same solvent of other ethylenic compounds is well-established to be stepwise.[32] This is fairly well consistent with the small kinetic and stereochemical sensitivity to substituent effects[25] and also with previous findings on hydrolysis of glycosyl derivatives.[29] More work is in progress to understand in more details the reaction mechanisms of glycals and related cyclic enol ethers and their differences with those established from more usual ethylenic compounds.

Experimental Section

^{1}H and ^{13}C NMR spectra were registred in $CDCl_3$ containing TMS as the internal reference. All solvents were reagent grade and were used without further purification. Commercial tri-*O*-benzyl-D-glucal (97%), tri-*O*-benzyl-D-galactal (98%), tri-*O*-acetyl-D-glucal, tetrabutylammonium tribromide (98%), bromine (1 mL sealed ampules), iodine monochloride, sodium azide, 2-benzoylbutyric acid and 2-hydroxymethyl-3,4-dihydro-2*H*-pyran were used as supplied.

2-Phenyl-*δ*-valerolactone[33] (8). To a water (23 mL) solution of benzoylbutyric acid (**6**) (2.1 g, 10.92 mmol) containing NaOH (5%) was added 0.5 g of solid $NaBH_4$ (13.21 mmol), and the reaction mixture was stirred at room temperature for 6 h. After 20 h at room temperature, $CHCl_3$ (25 mL) was added, and the aqueous phase was acidified by addition of HCl. The aqueous phase was then extracted with $CHCl_3$ (3 × 5 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The crude product[34] (**7**) (2.07 g) was pyrolized at 80−106 °C in vacuo, collecting the water in a Dean−Stark trap. Recrystallization from diethyl ether gave 1.46 g of compound **8** as a crystalline solid (78% yield). ^{1}H NMR ($CDCl_3$, *δ* ppm): 7.32 (5H), 5.32 (dd, *J* = 10.2, 3.2 Hz, 1H), 2.51−2.65 (m, 2H), 1.79−1.98 (m, 4H). ^{13}C NMR ($CDCl_3$, *δ* ppm): 171.2, 139.4, 125.4−128.2, 81.3, 30.1, 29.1, 18.2.

2-Phenyl-*δ*-valerolactol[33] (9). To a solution (95 mL) of 2-phenyl-*δ*-valerolactone (**8**) (1.45 g, 8.3 mmol) in dry CH_2Cl_2 was added DIBAL-H (10.5 mL, 1.0 M in hexane) at −78 °C. The reaction mixture was stirred for 2 h, quenched with a saturated aqueous $NaHCO_3$ solution (30 mL), diluted with 20 mL of CH_2Cl_2, and warmed at room temperature under magnetic stirring. After washing with an aqueous solution of HCl 10% and NH_4Cl (1:1.5), the organic phase was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 1.68 g of lactol **9** (94%) as a white crystalline solid. ^{1}H NMR ($CDCl_3$, *δ* ppm): 7.1−7.5 (5H), 5.39 (s, 1H), 4.99 (dd, 1H, *J* = 2.3 Hz), 4.78 (d, 1H, *J* = 9.6 Hz), 4.43 (d, 1H, *J* = 9.8 Hz), 1.36−2.06 (m, 6H). ^{13}C NMR ($CDCl_3$, *δ* ppm): 126.5−128.9, 97.4, 92.8, 79.1, 71.5, 18.4−34.2.

2-Phenyl-3,4-dihydro-2*H*-pyran[35] (5). To a solution of **9** (1.2 g) in dry toluene (45 mL) was added P_2O_5 (8 mg), and the solution was allowed to reflux for 2 h. After being cooled at room temperature, the reaction mixture was washed with an aqueous solution of $NaHCO_3$ and the organic phase was dried over anhydrous $MgSO_4$. Filtration and concentration of the filtrate in vacuo provided 1.08 g of a crude residue wich was chromatographed on a silica gel column. Elution with hexanes−ethyl acetate (8:2) gave 500 mg of pure **5** (46%). ^{1}H NMR ($CDCl_3$, *δ* ppm): 7.23−7.37 (5H), 6.53 (d, 1H, *J* = 6.09 Hz), 6.74−4.85 (m, 2H), 1.9−2.05 (m, 4H). ^{13}C NMR ($CDCl_3$, *δ* ppm): 144.1, 141.9, 128.3, 125.8, 100.6, 77.0, 30.2, 20.2.

2-Benzyloxymethyl-3,4-dihydro-2*H*-pyran[36] (4). To a solution of 2-hydroxymethyl-3,4-dihydro-2*H*-pyran (1.37 g, 12 mmol) in 26 mL of THF containing 0.5% of H_2O were added 138 mg (0.52 mmol) of 18-crown-6 and 2.6 g of powdered KOH. The mixture was stirred at room temperature for 20 min, and 1.5 mL (12 mmol) of benzyl bromide was added. After 24 h at the same temperature, 6 mL of MeOH was added. The reaction mixture was stirred for 10 min, and the solvent was evaporated under reduce pressure to give a residue which was diluted with 100 mL of CH_2Cl_2. The organic phase was washed with water, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on a silica gel column. Elution with hexane−ethyl acetate (7:3) gave 1.78 g of pure 2-benzyloxymethyl-3,4-dihydro-2*H*-pyran (**4**). ^{1}H NMR ($CDCl_3$, *δ* ppm): 7.34−7.4 (m, 5H), 6.42 (d, *J* = 6.2 Hz), 4.8−4.5 (m, 3H) 4.04 (m, 1H), 3.57 (ddd, 2H), 1.4−1.2 (m, 4H). ^{13}C NMR ($CDCl_3$, *δ* ppm): 143.5, 138.1−127.6, 100.4, 74.0, 73.3, 72.4, 24.5−19.3.

Additions of ICl and NaN_3. Iodine monochloride (0.55 mmol) was added to a suspension of 1.5 mmol of NaN_3 in 2.5 mL of CH_3CN cooled at 0 °C. After 10 min, the cyclic enol ether (**4** or **5**) (0.5 mmol) dissolved in 2.5 mL of the same solvent and precooled at 0 °C was added. The mixture was stirred at 0 °C for 15 min, diluted with a 10% of aqueous $NaHSO_3$, extracted with CH_2Cl_2, dried, and evaporated. The crude residue was analyzed by ^{1}H and ^{13}C NMR. All experiments were carried out at least in triplicate.

Additions of Bromine and Bu_4NBr_3. (a) In 1,2-Dichloroethane. 1,2-Dichloroethane solutions of Br_2 or Bu_4NBr_3 (5 mL, 10^{-2} M) were mixed with 5 mL of a 10^{-2} M solution of **2**, or **3**, or **4** or **5** in the same solvent. After the rapid disappearance of color the mixture was evaporated (washed with water for the Bu_4NBr_3 reactions) and the residue was analyzed by ^{1}H and ^{13}C NMR.[37] All experiments were carried out at least in triplicate.

(b) In Methanol. The bromination in MeOH was carried out in the same way as bromination in 1,2-dichloroethane. At the end of reaction the mixture was diluted with water, extracted with CH_2Cl_2, and analyzed by ^{1}H and ^{13}C NMR.[37] All experiments were carried out at least in triplicate.

(c) In Methanol, in the Presence of NaN_3. To solutions of NaN_3 (0.1−0.285 M) in methanol (20 mL), containing the glycal (1×10^{-2} M), an equivalent of bromine in same solvent (1 mL) was added under stirring and the reaction mixtures were stored in the dark at 25 °C. After the rapid disappearance of color the reaction mixtures were diluted with water and the products were extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), evaporated in vacuo, and analyzed by ^{1}H and ^{13}C NMR. Dibromo adducts were always insignificant. All experiments were carried out at least in triplicate.

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Supporting Information Available: ^{1}H and ^{13}C NMR data of adducts **a**, **b**, and **c** (Table S1). ^{1}H and ^{13}C NMR spectra (Figures S1−S9) of adducts **a**, **b**, and **c** from **3**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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