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Dissecting the essential role of anomeric ****-triflates in glycosylation re- actions

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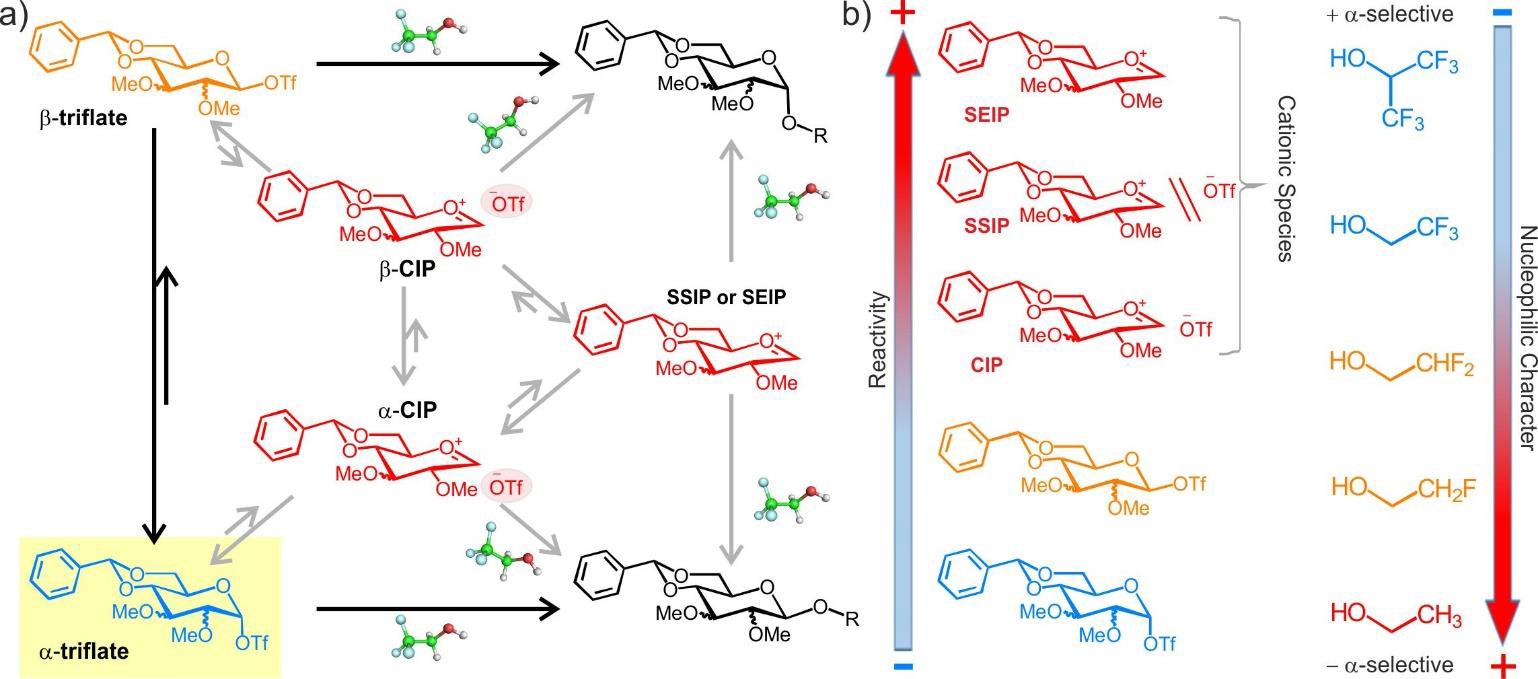
*Glycosylation Mechanism, -glycosyl triflates, Triflate Anomerization, Close ion pair, Reaction Kinetics, NMR.*

**ABSTRACT:** Glycosylations promoted by triflate-generating reagents are widespread synthetic methods for the construc- tion of glycosidic scaffolds and glycoconjugates of biological and chemical interest. These processes are thought to proceed with the participation of a plethora of activated high energy intermediates such as the - and -glycosyl triflates, or even increasingly unstable glycosyl oxocarbenium-like species, among which only -glycosyl triflates have been well character- ized under representative reaction conditions. Interestingly, the remaining less accessible intermediates, yet to be experi- mentally described, seem to be particularly relevant in -selective processes, involving weak acceptors. Herein, we report a detailed analysis of several paradigmatic and illustrative examples of such reactions, employing a combination of chemical, NMR, kinetic and theoretical approaches, culminating in the unprecedented detection and quantification of the true - glycosyl triflate intermediates within activated donor mixtures. This achievement was further employed as a stepping-stone for the characterization of the triflate anomerization dynamics, which along with the acceptor substitutions, govern the stereochemical outcome of the reaction. The obtained data conclusively show that, even for highly dissociative reactions involving -Close ion pair (-CIP) species, the formation of the -glycoside is necessarily preceded by a bimolecular → triflate interconversion, which under certain circumstances does become the rate-limiting step. Overall, our results rule out the prevalence of the Curtin-Hammett fast-exchange assumption for most glycosylations and highlight the distinct reactivity properties of - and - glycosyl triflates against neutral and anionic acceptors.

The acknowledgment of the relevance of glycoconju- gates in biological processes has run parallel to the devel- opment of new methods for glycosidic bond formation.1-9 Thus, the last few decades have witnessed a burgeoning progress in the area of glycosyl donor engineering, with a more recent focus on the understanding of glycosylation mechanisms.10-15 Central to many of these processes is the role played by glycosyl triflates. These highly reactive species are formed upon activation of common sugar do- nors, such as glycosyl sulfoxides or thio-glycosides among others,16 and are believed to exist as a mixture of - and - anomers in a fast exchange equilibrium. Both of them can, in turn, participate in nucleophilic substitutions with alco- hol acceptors through a continuum of mechanisms span- ning the gap between pure SN2 and SN1 processes, as shown by extensive studies performed by Crich and col.10 Owing to stereoelectronic and polar considerations, equa- torially oriented anomeric triflates display a decreased stability with respect to their axial counterparts, as dictat-

ed by the anomeric effect.17 However, while -triflates are, at best, marginally populated, they can still play key roles in glycosylations due to their much enhanced reactivity. Indeed, a Curtin-Hammett scenario, implying a rapid / triflate interconversion on the reaction time-scale, has been traditionally invoked to describe glycosidic bond formation and to explain the stereoselectivity of the pro- cess (Figure 1a).10 A paradigmatic example of this is pro- vided by the diverging - and - selectivity observed in glycosylations with 4,6-*O*-benzylidene-protected D- glucopyranosyl and D-mannopyranosyl donors, respective- ly.

According to current knowledge, the decreased stabil- ity/population of the -triflate intermediate for mannose derivatives, disfavored both by the anomeric effect and by repulsive dipolar interactions with the axial substituent at C2, would effectively minimize any Curtin-Hammett kinetic scheme, thus determining the preferential formation of the



**FIGURE 1.-** a) Schematic representation of the multiple SN2/SN1 reaction pathways leading to the formation of - and -glycosides from glycosyl triflate intermediates. CIP, SSIP and SEIP stand for contact ion pair, solvent separated ion pair, and solvent equili- brated ion pair, respectively. b) Reactivity gradient for the potential donor intermediates and acceptor alcohols. Glycosylations with weakly nucleophilic alcohols proceed with increased -stereoselectivity.

-product via the major -triflate.10 On the contrary, anal- ogous glucose donors would evolve through a more acces - sible -triflate to yield the corresponding inverted - products. Interestingly, chemical glycosylations with poor- ly nucleophilic acceptors seem to proceed, in all cases, with an enhanced -selectivity as shown by Codée and col., which could reflect the dominant role played in these cir- cumstances by the minor, yet more reactive intermediates, such as -triflates or even glycosyl oxocarbenium-like species present in the reaction mixture (Figure 1b).11a

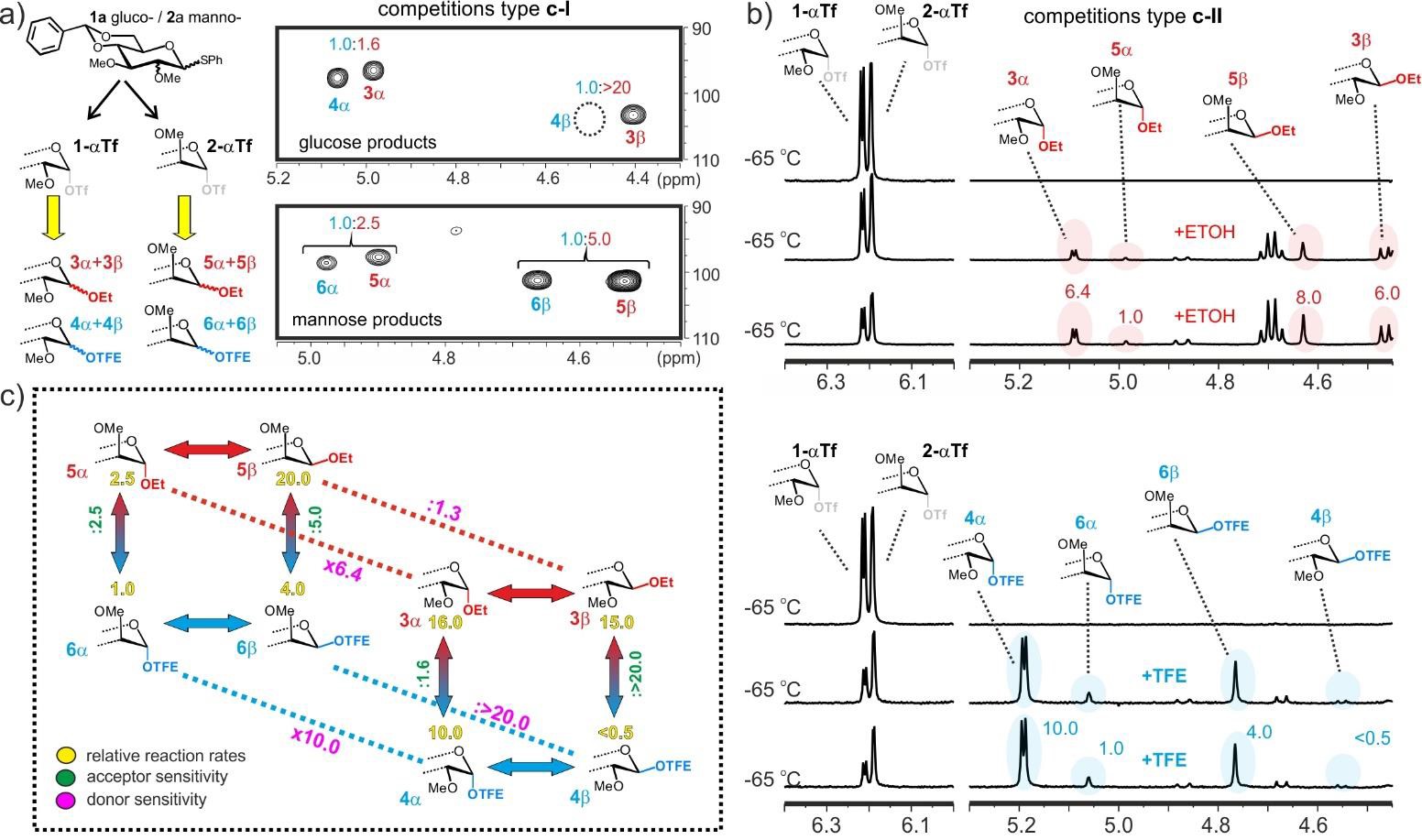
Notwithstanding the wide relevance of anomeric tri- flates in glycochemistry, very little is known about the anomerization process and its potential impact on the glycosylation outcome. More specifically, the NMR detec- tion of the highly unstable equatorially oriented triflates has represented a significant challenge in itself, and just one example, involved in a conformational rather than an anomerization equilibrium, has been confidently reported so far.18 On the other hand, key aspects of the mechanism, including triflate /exchange rates or their substitution kinetics by an alcohol, have proven inaccessible to the chemical community under direct experimental scrutiny, due to the marginal population and high reactivity of some of the species involved (Figure 1). In fact, it is important to emphasize that, in the absence of more detailed infor- mation, the general prevalence of Curtin-Hammett’s condi- tions for these processes should be considered a mechanis- tic assumption. To address these issues, we have carried out a comprehensive analysis of anomeric substitutions involving - and - triflate species, focusing our attention on those reaction pathways that determine the formation of a major -glycoside from a seemingly exclusive - glycosyl triflate intermediate. With this objective in mind, we have employed a multidisciplinary approach compris- ing the extensive use of variable temperature NMR (vt- NMR) on both unlabeled and isotopically labeled samples, as well as competition and kinetics experiments, high-level

computational chemistry calculations and preparative scale reactions.

#### RESULTS

***Experimental determination of relative glycosylation rates.-*** From a chemical perspective, the divergent stere- oselectivities observed for the 4,6-*O*-benzylidene- protected epimeric donors **1a** and **2a** must reflect the distinct rates that characterize the alternative reaction pathways represented in Figure 1a. While a complete picture of the operating glycosylation mechanism is diffi- cult to draw, relative formation rates for the /products can, in principle, be estimated by straightforward competi- tion experiments. In order to gain insight into the differen- tial reactivity and properties of the glucose/mannose dyad (**1a** vs **2a**), two complementary assays (herein referred to as ***c-I*** and ***c-II***) were carried out, employing low tempera- ture NMR:

* In competitions type ***c-I***, glycosyl triflates derived from **1a** or **2a** (in separate assays), were treated with an equi- molecular binary mixture of competing alcohols, compris- ing a good nucleophile (ethanol) and a weakly nucleophilic acceptor (trifluoroethanol) (Figure 2a). This kind of assays reveals the acceptor sensitivity displayed by each triflate. It is worth mentioning that analogous experiments were originally employed by Sinnott and col. for the study of glycoside solvolysis reactions and have since been used by other authors in different contexts.19
* On the contrary, in competitions type ***c-II***, an equimo- lecular mixture of competing triflates, derived from **1a** and **2a**, was treated with a sub-stoichiometric amount of a given acceptor alcohol, either ethanol or trifluoroethanol (in separate experiments) (Figure 2b). Under these exper- imental conditions, we should be able to determine the relative donor reactivity for each acceptor alcohol.



**FIGURE 2.-** a) Competitions type ***c-I***. The obtained glycoside mixtures were analyzed by means of 1D or 2D-HSQC experiments (anomeric region shown). Relative populations are indicated. b) Competitions type ***c-II*** carried out employing ethanol (upper pan- els) and trifluoroethanol (lower panels) as acceptors. For each alcohol two consecutive sub-stoichiometric additions were per- formed. Relative populations for the alternative glycoside products are shown. c) Chart showing the combined values obtained from competitions ***c-I*** and ***c-II*** that allowed estimating the relative formation rates for the eight possible glycosylation products (in yellow), together with the ratios representing the acceptor and donor sensitivities (in green and magenta, respectively).

Under the employed conditions, every single experiment (either ***c-I*** or ***c-II***) yielded a mixture of four glycosylation products whose populations, determined through 1D or 2D-HSQC experiments, reflect their relative formation rates. Altogether, this experimental data set allowed us to build a simple chart for the eight possible glycosides gen- erated (Figure 2c), and the main conclusions thereof are summarized in the following points:

1. Regarding -glycosylations, the replacement of etha- nol by the weaker trifluoroethanol determines, in all cases, the expected reduction in the corresponding reaction rates (**3**vs **4**and **5**vs **6**). Interestingly, this effect is much more pronounced for the glucose case (>20-fold), where the TFE-derived -product was barely detectable in the reaction mixtures. On the contrary, both -glycosylations seem fairly insensitive to the nucleophilic character of the acceptor alcohol, with relative rate decreases in the 1.6-2.5 range (**3**vs **4**and **5**vs **6**). These latter results are fully consistent with experimental observations reported by Codée and col. according to which -stereoselectivity increases for poor acceptors, and points to the involve- ment of more reactive species, either -triflates or glycosyl oxocarbenium ions, in the reaction.11
2. With nucleophilic acceptors such as ethanol, both glu- co- and manno- -glycosides form with nearly identical rates (derivatives **3**vs **5**). This is an unexpected conclu- sion, given the well-known -selectivity of mannosyl tri-

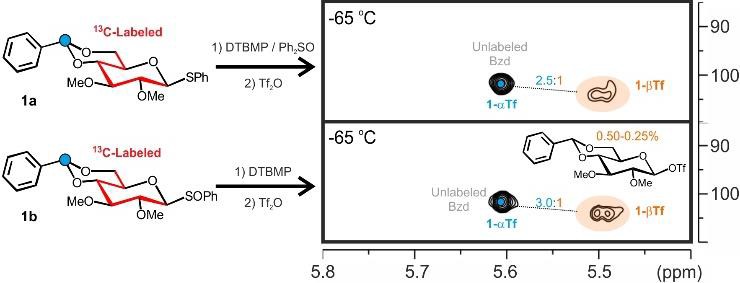
flates in contrast with the -selectivity of its glucosyl coun- terpart. Therefore, the reason for the diverging stereo- chemical outcome of these two donors has to come from the -glycosylation process, which indeed is significantly faster for the glucose derivative (ca. 6-fold, **3**vs **5**), a trend that is further accentuated in the presence of weak alcohols (ca. 10-fold, **4**vs **6**).

To conclude, these initial studies confirm that the con- figuration of position 2 of the sugar donor is key in modu- lating the stereoselective outcome of the glycosylation process, probably by affecting the stability/population of the corresponding -glycosyl triflates, and further sup- ports the participation of such intermediates in the process of -glycosylation.

***A comprehensive NMR analysis of the anomeric sub- stitution of glucosyl triflates by poor acceptors.-*** With the results from the previous section in hand, we focused our attention on the intriguing behavior displayed by glu- cosyl donor **1a** with trifluoroethanol. As shown in Figure 2, this particular glycosylation proceeds with a total stere- oselectivity to render an exclusive -adduct from a pre- dominant -triflate intermediate, which would make the involvement of a highly reactive -species even more rele- vant in this case. Importantly, while the existence of a - glucosyl triflate has often been postulated, to the best of our knowledge, it has neither been detected, nor quantified before. Taking this into consideration, we first decided to

have a closer inspection at the triflate mixtures generated from glucosyl donors under different glycosylation condi- tions.

*NMR detection of the -glucosyl triflate intermediate.-* In order to increase the chances to detect the key -triflate intermediate, we resorted to 13C-labeled samples. Thus, both the thio-phenyl derivative **1a** and the corresponding sulfoxide **1b** were synthesized from 13C-glucose and pre- activated at low temperature. The resulting solutions were analyzed by means of HSQC experiments (Figure 3a) and revealed the presence of an apparently exclusive -triflate species (>99%), in agreement with previous reports.10,16 In fact, despite the extra sensitivity provided by the isotopi- cally labeled samples, significant accumulation times were required before an anomeric cross-peak could be confi- dently assigned to a -triflate intermediate. This signal appears at H = 5.48 ppm, around 0.6 ppm up-field shifted with respect to that of the major derivative and presents a C value of 104 ppm in chloroform. In addition, both the homonuclear proton-proton (3JHH = 7.2 Hz) and the het- eronuclear proton-carbon (1JHC = 177 Hz) coupling con- stants are in agreement with the equatorial orientation of the anomeric substituent. Satisfactorily, this result was successfully reproduced regardless of the activation proto- col employed, inherent to each donor type (thio-phenyl or sulfoxide donors, **1a** and **1b**). Finally, from the intensity of the detected cross-peaks, the -triflate population was estimated between 0.25 and 0.50 %, consistent with a K equilibrium constant in the 2.5 10-3-5.0 10-3 range, which corresponds to a free energy difference of 2.3±0.15 kcal/mol at -65 oC between the and triflate.



**FIGURE 3.-** HSQC experiments acquired with triflate mixtures generated upon activation of 13C-labeled donors **1a** and **1b**. Cross-peaks corresponding to the (unlabeled) benzylidene CH fragment in the major -glucosyl triflate intermediate (in cyan), and the 13C-labeled anomeric CH group in the corre- sponding -glucosyl triflate (in orange) are shown. Peak rela- tive ratios, together with the estimated population for the - derivative are indicated.

*Kinetics of the -glucosylation process with poor accep- tors.-* The time evolution of the glucosyl triflate mixtures upon addition of trifluoroethanol was analyzed next. This represented a significant challenge from an experimental perspective, given the high reactivity and reduced stability of the triflate intermediates. However, a careful experi- mental design allowed us to handle these solutions with minimal temperature fluctuations during the whole pro- cess, particularly during the critical steps of adding the acceptor alcohol and mixing the resulting solution. Never- theless, as an extra precaution to minimize the impact of any potential temperature changes on the reaction time courses, the first data point recorded in each experiment

was discarded by default, and the initial concentrations reset accordingly.

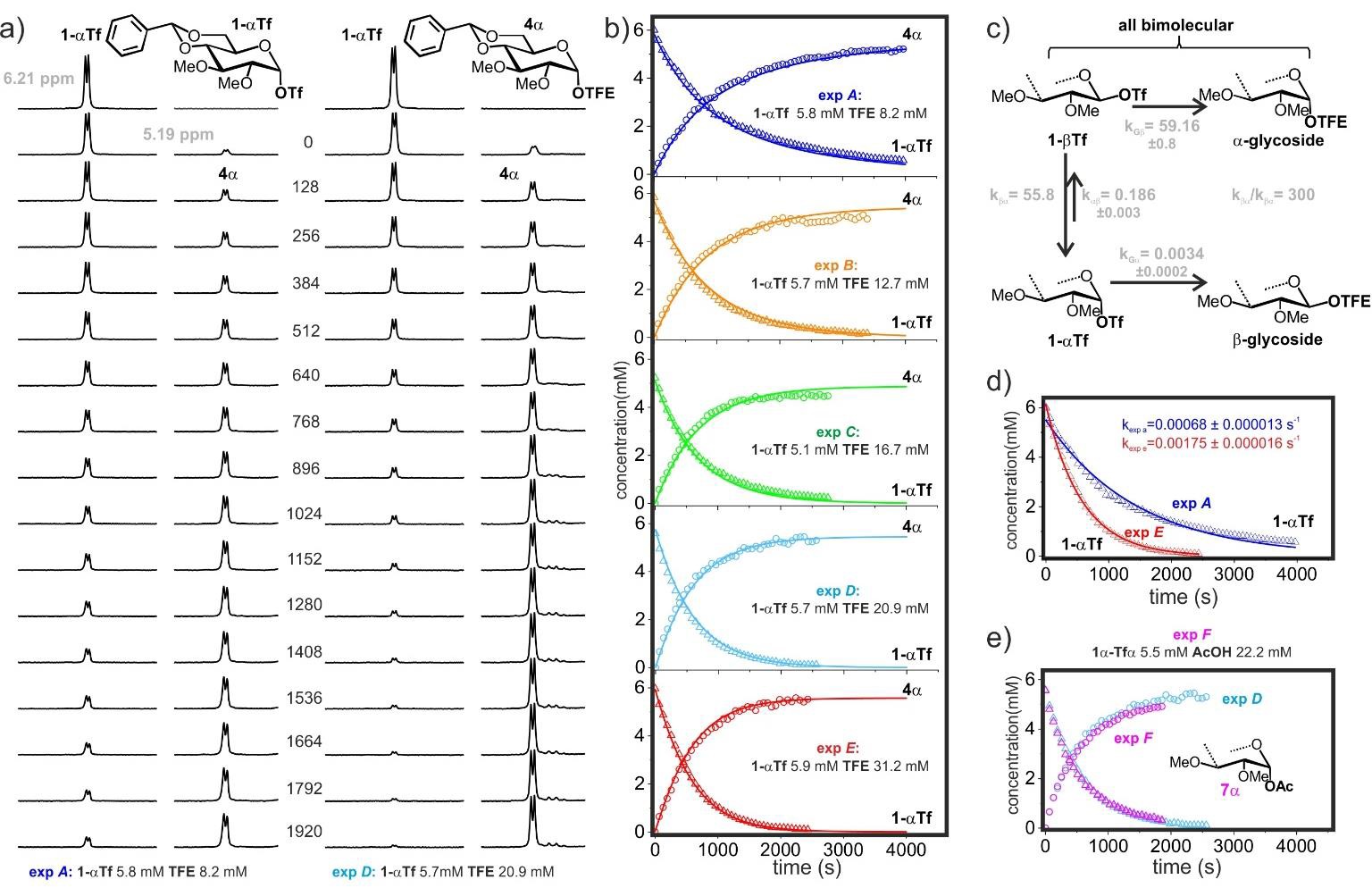
Reactions were performed with increasing concentra- tions of trifluoroethanol (TFE), herein referred to as exper- iments ***A***-***E***, and monitored through sequential 1D-NMR spectra. Selected data sets, together with all reaction curves derived for this donor/acceptor pair, are shown in Figures 4a and b, respectively (see also: Figure S1). A visu- al inspection of curves ***A*** and ***B*** reveals that the process becomes faster with the acceptor concentration. Intri- guingly though, this acceptor sensitivity diminishes in experiments ***B***-***C***, and totally vanishes for reactions ***D***-***E*** carried out with the highest trifluoroethanol/donor ratios (Figure 4b-d). Such observations seem inconsistent with the assumption of either a simple bimolecular or uni- molecular mechanism, and points to a more complex sce- nario for the formation of the -glycoside. Indeed, at- tempts to analyze the obtained curves assuming a first order process yielded a poor fitting for data set ***A***, which progressively improved for curves ***B***-***E*** (Figures 4d and S2).

In view of these results, the experiments were re- examined in a more elaborate fashion, fully assuming the kinetic model represented in Figure 4c, which involves triflate anomerization prior to substitution of the resulting

-derivative with trifluoroethanol. Therefore, the system is defined by four rate constants, herein referred to as k and kfor triflate anomerization, and kGand kGfor the alcohol substitution processes of each individual glucosyl- triflate. A least-squares fitting of the ten reaction curves was simultaneously performed with the program Dynafit20 to determine the set of constant values which better agrees with all the experimental information available. Consider- ing the significant nucleophilic character exhibited by triflate anions in organic solvents,21 the anomerization step was assumed to be bimolecular, and the k/kratio was constrained to the experimentally determined value (K

=3.3 10-3). Regarding the second step, both zero and first order kinetics in the alcohol were explicitly considered, but only the second mechanistic assumption produced satisfactory results (see Figures S3 and 4b, respectively). According to these data, the substitution of the -glucosyl triflate with the acceptor alcohol is much slower than its conversion into the more reactive -triflate (kG<< k), which is in agreement both with the negligible fraction of

-glycoside product generated in the process, and also with the higher nucleophilic character of the triflate anion with respect to trifluoroethanol.21 On the contrary, the highly reactive -triflate intermediate shows no preference for any of these two species (kG~ k), in line with the behavior observed in the ethanol/trifluoroethanol compe- titions ***c-I*** (vide supra). Strikingly, the resulting scenario, built on the obtained set of kinetic constants, does not satisfy Curtin-Hammett conditions, for which triflate ex- change should be much faster the acceptor substitutions (k>> kGand k>>kGAs a consequence, the /ratio for triflate intermediates cannot remain constant through- out the reaction, and so it must evolve during the process. More importantly, the global reaction rate can increase with the acceptor concentration up to a limit in which triflate anomerization becomes rate-limiting. In agree- ment with this view, glycosylations with TFE in the



**FIGURE 4**.- a) Time evolution of **1-Tf** in CDCl3 at -65 oC upon addition of trifluoroethanol (experiments ***A*** and ***D***). b) Experimental reaction curves (circles and triangles) derived from experiments ***A***-***E***. The solid lines represent the simultaneous least-squares

fitting of the ten curves to the kinetic model shown on panel c. c) Kinetic model employed for the analysis of the experimental reaction curves. The resulting kinetic constants are represented in grey. During the fitting procedure the k/kratio was con- strained to the experimentally determined range. d) First order fitting of reaction curves for the consumption of **1-Tf** in experi- ments ***A*** and ***E***. e) Experimental curves for experiment ***D*** superimposed on that derived from experiment ***F*** employing acetic acid as acceptor to yield derivative **7**.

presence of additional triflate anion revealed a clear en- hancement in the reaction rates which must partially re- flects a faster anomerization process. Interestingly, these data sets also suggest additional activating effects of the triflate on the alcohol substitution step (Figure S4). Indeed, a catalytic influence of triflate anions on glycosylation processes has been recently reported.14b

This similar reactivity deduced for trifluoroethanol and anionic triflate against the -glucosyl triflate is intriguing and made us wonder whether the same behavior stands for even weaker nucleophiles. With this idea in mind, we performed additional assays employing acetic acid as ac- ceptor (Figure 4e, experiment ***F***; this assay did not include any base in the reaction mixture to ensure that no acetate form was present). Under these conditions, we observed that the reaction proceeds with total stereoselectivity to yield a sole -*O*-acetyl-glycoside and that the obtained kinetic curves were almost identical to those previously recorded with a comparable concentration of trifluoroeth- anol (experiment ***D***), strongly suggesting a common reac- tion pathway (Figures S5).

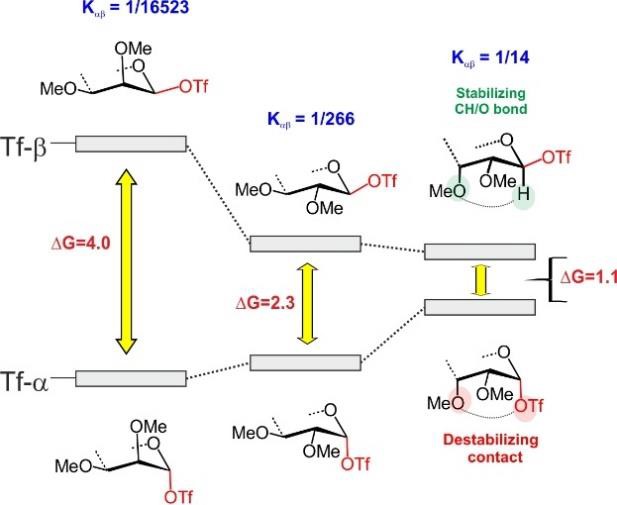
While this model-based interpretation of the experi- mental data is plausible, the marginal -triflate concentra- tion present in the reaction mixtures renders key parame- ters of the kinetic scheme (such as the anomerization rate

constants, kand k) inaccessible by direct experimental measurements, thereby precluding further validation of our conclusions. At this point, we reasoned that an ade- quate re-design of the donor substrate, aimed at increasing the -glycosyl triflate fraction in equilibrium, could pro- vide definite support for the proposed kinetic regime.

***Amplifying the -glycosyl triflate population through***

***-selective destabilizing interactions: the allose case.-*** In order to reduce the energy gap between both anomers, which ultimately determines the equilibrium populations, a simple strategy based on the destabilization of the - glycosyl triflate by means of an unfavorable 1,3-diaxial interaction with a properly oriented substituent was em- ployed. This approach was fully supported by quantum mechanics calculations carried out on the model structures (PCM(CHCl3)/M06-2X/6-31G(d,p)). Thus, according to theoretical data (Figure 5), the orientation of the C-2 sub- stituent of the pyranose exerts a substantial influence on the magnitude of the anomeric effect that decreases from manno- to gluco- configurations from 4.0 to 2.3 kcal/mol, in terms of free energy differences. It is worth mentioning that in the case of the glucose derivative, the calculated value shows a total agreement with the one experimentally estimated by us (2.3 kcal/mol; Figure 3).

As previously anticipated, the C-3 substituent offers the opportunity to further diminish the energy difference between anomers: an inversion of its orientation from equatorial to axial (such as in D-allose) leads to a severe polar/steric destabilization of the -triflate, which in turn is accompanied by a slight stabilization of the -anomer via a non-canonical CH/O hydrogen bond (Figure 5).



**FIGURE 5**.-Free energy differences between - and -glycosyl triflates for D-manno-, D-gluco- and D-allo-derivatives (in the gas phase) computed by quantum mechanics calculations (PCM(CHCl3)/M06-2X/6-31G(d,p)level). The predicted K equilibrium constants are represented in blue.

These combined effects would determine a sharp reduc- tion of the /triflate energy gap, which becomes proxi- mate to 1 kcal/mol and should therefore render the - triflate amenable to experimental detection and character- ization by NMR. Indeed, according to the obtained theoret- ical data, its population at -65 oC should be larger than 6%. The use of a larger basis set 6-311+G(2d,p), further in- creased the calculated stability of the -triflate to yield a

G of 0.1 kcal/mol, and a -triflate population around 45%.

*Detection of the allose -triflate intermediate and NMR characterization of the exchange dynamics.-* With this promising theoretical support in hand, we embarked in the preparation of D-allose donors **8a** and **8b**, which were pre- activated employing regular conditions. To our satisfac- tion, low temperature NMR experiments confirmed, in both cases, the presence of an equilibrium mixture com- posed of - and -triflates in a 2.7:1 ratio, respectively, corresponding to a G value of 0.4 Kcal/mol at -65 C (Figure 6a).

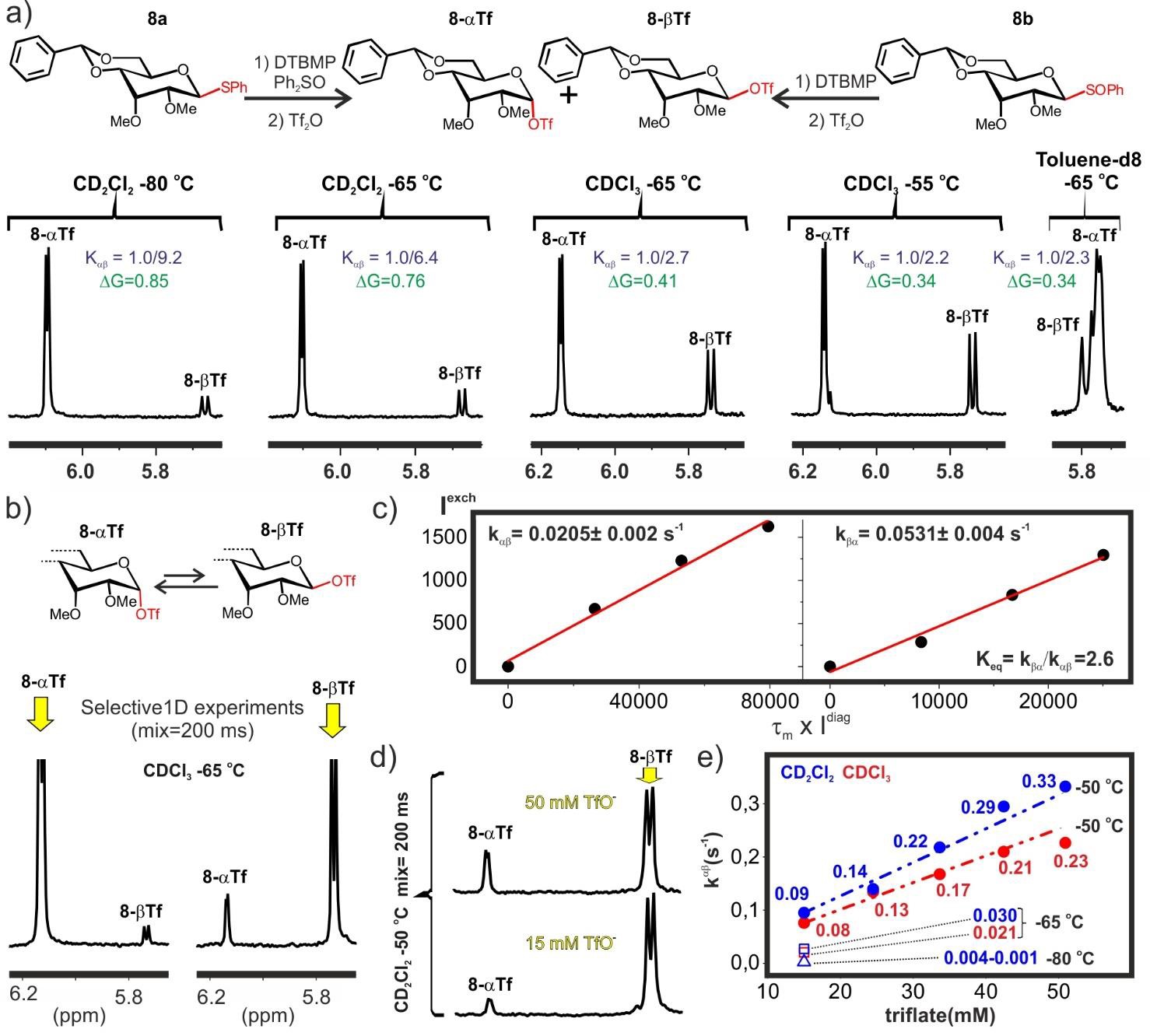
The signal of the anomeric proton of the -allosyl triflate appears at H = 5.74 ppm, ca. 0.3 ppm down-field shifted with respect to that previously detected for its glucose analog (Figure 3), probably reflecting its polar interaction with the axial methoxy group. However, both 3JHH and 1JCH constants for the anomeric position (Figure 6a) were fully consistent with those measured for the analogous -gluco- intermediate (8 and 178 Hz, respectively). Interestingly, all measurable 3JHH values are in agreement with a 4C1 con- formation for both anomers, evidencing no significant

distortions even for the -derivative, where a steric con- flict seems clearer (Figure S6). Additionally, to further interrogate this previously undetected anomerization equilibrium, both its temperature and solvent dependence were also studied. As expected, considering the reduced dipole moment exhibited by the -anomer, its molar frac- tion increases in low dielectric environments (from / 6:1 in CD2Cl2 to 2.3:1 in toluene-d8). Similarly, the / ratio at equilibrium is tilted in favor of the less stable - anomer at higher temperatures (Figure 6a). In summary, according to our data, the fraction of -triflate available for glycosylation shows a significant sensitivity to the experi- mental conditions employed, being the solvent polarity and the temperature two key parameters to consider.

The unusually large -triflate population exhibited by the allose system offered the possibility of characterizing, also for the first time, the glycosyl triflate exchange dynam- ics. This anomerization process is central to the Curtin- Hammett schemes typically invoked to explain glycosyla- tions. Fittingly, both 1D and 2D-EXSY experiments con- firmed the presence of exchange peaks between - and - triflate intermediates, which allowed the determination of the corresponding rate constants under a variety of exper- imental conditions (Figure 6b-e).22 Both kand kwere independently measured following a protocol analogous to that described by Gschwind22a and Taylor,22b and the rate constant ratios (k/k) were found to be consistent with the corresponding experimental equilibrium constants (Keq).

Several conclusions can be obtained from these data. First, the exchange rates determined for D-allopyranosyl triflates in chloroform at -65 oC are one order of magnitude higher than those described for unconstrained glycopyra- nosyl mesylates at 25 C, which shows the extreme lability of the former reactive species (see Figure 6c and Table 1).22b Secondly, resulting from the increased polarity of dichloromethane, whose influence on triflate equilibrium is already clear (Figure 6a), the experimental exchange rate values derived in this media are slightly larger than those measured in chloroform. Further, this process shows a great sensitivity to temperature, becoming 5-fold faster by simply raising the temperature to -50 oC. Conversely, the obtained experimental data is consistent with an al- most 10-fold reduction in the exchange rate constant at - 80 oC in dichloromethane (Figures S7-S10).

Most importantly, experiments carried out in the pres- ence of increasing concentrations of tetrabutylammonium triflate (TBAOTf) at -50 C and at -65 oC demonstrated that the exchange kinetics depend linearly on the triflate anion concentration in both solvents, with a slope that fully sup- ports a bimolecular SN2-like anomerization mechanism (Figure 6d-e). This observation agrees with the significant nucleophilic character of triflate anions in apolar environ- ments21 and implies that the apparent exchange rates de- rived from EXSY NMR data using the initial rate approxi- mation22a correspond, in fact, to the product between the actual bimolecular constants and the concentration of triflate anion available for each assay (see the experi- mental section). Therefore, true SN2 rate constants (now expressed in M-1s-1) could be inferred, and the resulting values are also included in Table 1.



**FIGURE 6**.- a) Relative equilibrium concentrations for the - and -allosyl triflates (**8-Tf** and **8-Tf**) generated from donors **8a** or **8b**, under different solvent and temperature conditions, as revealed by 1D-NMR. The resulting Kand G (Kcal/mol) values are indicated. b) Example of selective NOESY-1D experiments acquired with excitation of either the or anomeric signals (left and right, respectively). c) EXSY plots. Linear fittings (red lines) provided the rate constants, which were independently deter- mined for the →and →processes (left and right, respectively). d) NOESY-1D experiments acquired with two different concen- trations of triflate anion. e) Anomerization rate constants determined under different experimental conditions (solvent, tempera- ture and triflate anion concentration).

As a final point, the relevance of the obtained values under actual glycosylation conditions was tested, for which hex- afluoroisopropanol (HFIP) was employed as the acceptor counterpart. By virtue of the slow progression of this reac- tion (vide infra), we were able to acquire quick EXSY NMR experiments during the process (Figure S11), showing that the triflate exchange dynamics previously described re- main basically unaltered in the presence of the acceptor alcohol.

*Chemical characterization of the allosyl donor: selectivity and reaction kinetics.-* The unusually large -triflate popu- lation exhibited by the activated **8a** donor mixtures would be expected to have a significant impact on its reactivity in glycosylations. Thus, we carried out assays with a selection

of representative weakly nucleophilic acceptors and the obtained results are compiled in Figure 7a. As it can be observed, the marked -preference exhibited by the anal- ogous glucose derivative with trifluoroethanol is slightly reduced in this case by the inversion of the pyranose posi- tion 3. This can be rationalized by an enhanced reactivity of the corresponding -allosyl triflate, now capable of reacting sluggishly with this alcohol (**10**:**10**8:1 com- pared with **4**:**4**>20:1). Nevertheless, as previously shown for the glucose/mannose case,11a further attenua- tion of the acceptor nucleophilic character (from trifluoro- ethanol to hexafluoroisopropanol or acetic acid) should favor -glycosidation, and indeed, in these two additional

**TABLE 1**.- a) EXSY kinetic constants (kexsy and kexsy, s-1) for the exchange between - and -allosyl triflates (**8-Tf** and **8-**

**Tf**) measured with different solvents (CDCl3 or CD2Cl2), temperatures (from -50 to -80 oC) and concentrations of triflate anion. The derived second order rate constants (kand k, M-1s-1) are also shown. Triflate concentrations are given in mM.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***CDCl3 -50 oC*** | | | | ***CD2Cl2 -50 oC*** | | | |
| **[TfO-]** | **kexsy** | **k** | **kexsy** | **k** | **kexsy** | **k** | **kexsy** | **k** |
| 15.0 | 0.076 |  | 0.177 |  | 0.095 |  | 0.330 |  |
| 24.5 | 0.134 | 4.21 | 0.315 | 9.86 | 0.140 | 7.02 | 0.483 | 19.3 |
| 33.6  42.4 | 0.168  0.210 | ±0.39 | 0.391  0.491 | ±0.91 | 0.218  0.295 | ±0.47 | 0.661  0.885 | ±0.99 |
| 50.9 | 0.227 |  | 0.530 |  | 0.333 |  | 0.998 |  |
|  | ***CDCl3 -65 oC*** | | | | ***CD2Cl2 -65 oC*** | | | |
| **[TfO-]** | **kexsy** | **k** | **kexsy** | **k** | **kexsy** | **k** | **kexsy** | **k** |
| 8.8 | 0.013 |  | 0.035 |  | - | - | - | - |
| 14.7  15.0 | 0.024  0.021 | 1.45 | 0.064  0.053 | 4.20 | - 0.030 | - 2.00 | - 0.192 | - 12.80 |
| 20.5 | 0.029 | ±0.10 | 0.078 | ±0.27 | - | - | - | - |
| 26.2 | 0.039 |  | 0.109 |  | - | - | - | - |
| 31.7 | 0.046 |  | 0.13 |  | - | - | - | - |
|  | **-** | | | | ***CD2Cl2 -80 oC (\*)*** | | | |
| **[TfO-]** | **-** | **-** | **-** | **-** | **kexsy** | **k** | **kexsy** | **k** |
| 15.0 | - | - | - | - | 0,0025\* (1-4 10-3) | 0.17 | 0.0225 | 1.50 |

*(\*)* Reduced exchange rates at -80 oC prevented an accurate measurement of the rate constants. Instead, a range estimate was determined.

cases the reaction proceeds with a total -stereoselectivity (Figure 7a).

Type ***c-I*** competitions with ethanol/trifluoroethanol mixtures revealed also a similar behavior to that observed for glucose and mannose derivatives: the - allosylationdisplays an almost null sensitivity to the accep- tor, while the -glycosylation remains significantly sensi- tive (Figure S12). On the other hand, competitions type ***c- II***, carried out with **1-Tf**/**8-Tf** triflate mixtures, showed that theformation rates of the allose products are at least 10-fold faster in comparison to those derived from glucose, regardless of the anomeric configuration of the product or the nature of the accepting alcohol. Overall, this reactivity enhancement must be reflecting both the destabilizing influence exerted by allose axial substituent on the - triflate, and the concomitant growth in the -triflate popu- lation.

Next, we analyzed the time evolution of the allose triflate mixtures upon addition of poor acceptors, such as trifluo- roethanol or acetic acid at -65 oC in chloroform. The ob- tained results are represented in Figures 7b and S13-S14 (experiments ***G***-***H***) and highlight several key features of the glycosylation process. Thus, the ratio between - and

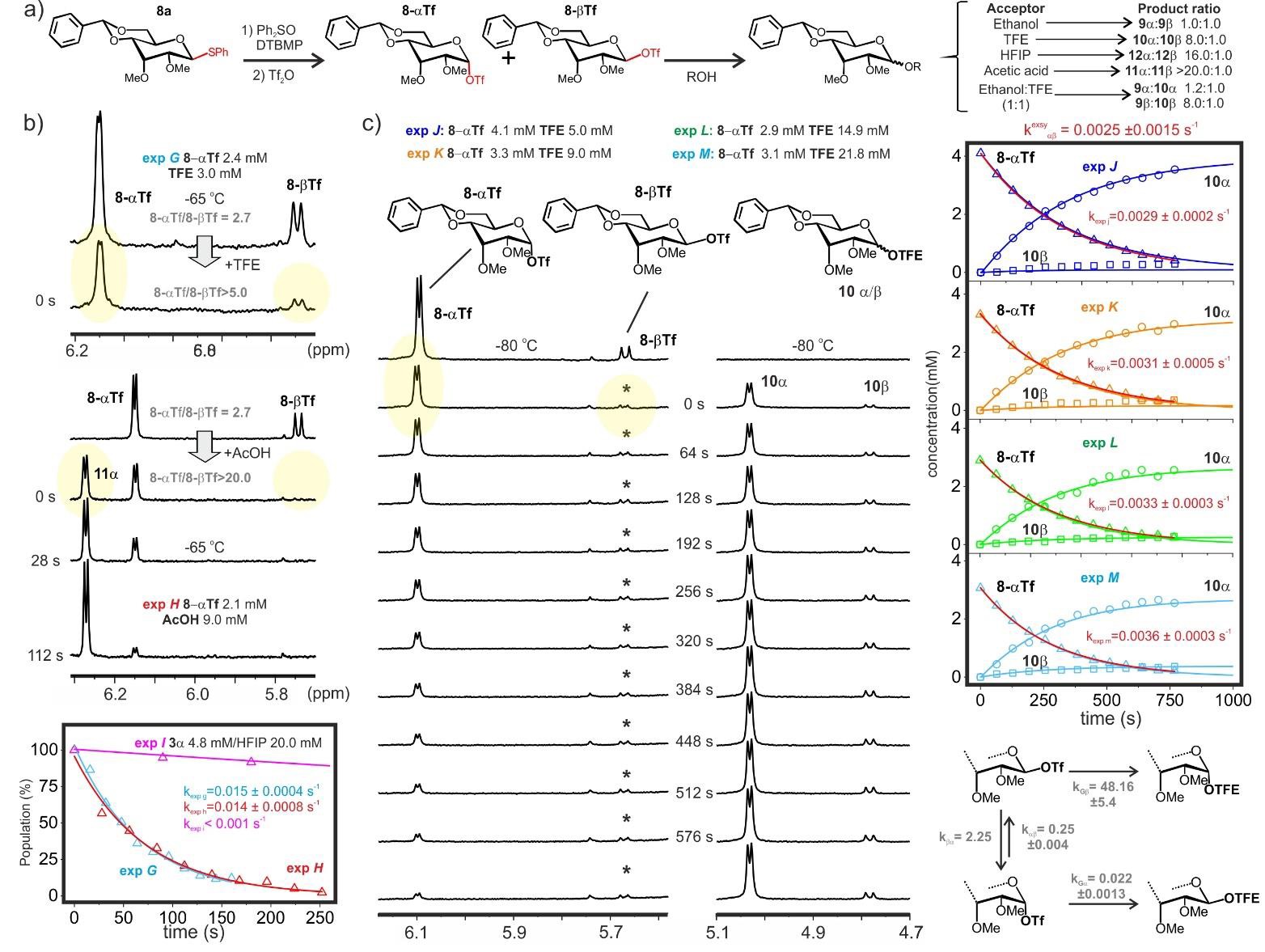
-triflate populations is not maintained throughout the experiment, owing to the fact that the minor -triflate is preferentially consumed, at a rate too large to permit its monitorization by NMR. This observation shows that the reactivity difference between both anomers is significant despite the relatively small energy gap between them. Most importantly, the substitution of the -triflate by the acceptor must be faster than the triflate anomerization, thus confirming that the glycosylation process cannot be described in terms of the Curtin-Hammett principle, as previously deduced for glucose donors.

The integration of anomeric signals for both the - triflate intermediate and the products allowed us to build the corresponding reaction curves (Figure 7b). Interesting- ly, first-order analysis of these data sets yielded good fit- tings with rate constants highly similar to those previously derived for the →anomerization process (0.014-0.015 vs 0.013-0.024 s-1. See Table 1). This experimental evi- dence establishes a mechanistic connection between the formation of the -glycoside and the triflate exchange process and supports the notion that this latter step must be both essential and rate-limiting.

Conversely, glycosylation assays with the extremely de- activated HFIP (experiment I) evolve at a much-reduced rate, although with an exquisite -stereoselectivity. Mean- ingfully, the relative populations of the - and -allosyl triflates remain unaltered throughout the reaction. These combined observations have two key mechanistic implica- tions: on the one hand, the substitution of the -triflate intermediate with this alcohol is slower than the exchange between allosyl triflates, in a way that the whole process now satisfies Curtin-Hammett requirements (see Figure S15). It should be noted though that this behavior is anec- dotal and will certainly not hold for most of the alcohols commonly employed in glycosylation reactions. On the other hand, the conversion of the -triflate into the major

-product is shown to respond to the substantial attenua- tion of the nucleophile (TFE vs HFIP), a plausible argument in favor of a bimolecular-like behavior for substitution mechanism during this step.

Given the high reactivity exhibited by the allose donor with trifluoroethanol, we decided to carry out additional assays at even lower temperatures (-80 oC in CD2Cl2). These experimental conditions determined a slower pro- gression of the reactions, allowing a more adequate



**FIGURE 7**.- a) Product ratios obtained upon treatment of triflates **8-Tf** + **8-Tf** with different acceptors or acceptor mixtures (competitions type ***c-I***, last entry). b) Kinetics experiments ***G***-***I*** (initial **8-Tf** and acceptor concentrations indicated) performed in CDCl3 at -65 oC. Selected 1D data sets, before and after addition of the acceptor (TFE or acetic acid), are shown. The anomeric tri- flate ratios (represented in grey) reveal the preferential consumption of the -stereomer by the acceptor. Reaction curves for the consumption of the major -allosyl triflate **8-Tf**, together with the corresponding first-order fittings and rate constants derived thereof are shown at the bottom. c) Kinetics experiments ***J***-***M*** performed in CD2Cl2 at -80 oC (initial **8-Tf** and acceptor concentra- tions indicated). The time evolution of the allosyl triflate mixture in experiment ***J*** as monitored by 1D NMR is displayed on the left. Reaction curves derived from experiments ***J***-***M*** are represented on the right. First-order fittings and rate constants are shown in red. The solid colored lines represent the simultaneous least-squares fitting of the twelve curves to the kinetic model shown at the bottom-right corner. The resulting kinetic constants are represented in grey.

monitorization of the experimental time courses. Analo- gously to the glucose case, reaction curves were derived at increasing concentrations of the acceptor alcohol (herein referred to as experiments ***J***-***M***). The obtained results rep- resented in Figures 7c and S16-S17 were consistent with the qualitative description of the glycosylation reaction previously outlined. Consequently, the -triflate interme- diate is preferentially consumed in all cases. Moreover, individual first order analysis of the reaction curves (either for the consumption of the -allosyl triflate or the for- mation of the -product) renders rate constants in the range of those previously measured for the triflate ex- change under similar experimental conditions (Table 1). Furthermore, the reaction rate shows only a slight sensitiv- ity to the acceptor concentration, which for the dominant

-anomer could be attributed to the rate-limiting character

of the preceding anomerization step, although a more SN1- like alcohol association cannot be ruled out either.

In order to derive the set of kinetic constants that better reproduces all the experimental data, the obtained reac- tion curves were simultaneously fitted to the more elabo- rate kinetic scheme shown in Figure 7c. According to pre- vious experimental evidences, we decided to consider both SN2 and SN1 scenarios for the alcohol substitution reac- tions. Contrarily, the exchange between and allosyl- triflates was taken as a pure SN2 process, in accordance with the linear dependence on the triflate concentration revealed by NMR data previously shown (Figure 6e and Table 1). Therefore, the corresponding kinetic constants for this latter step (kand k) were constrained to the experimentally derived values during the fitting proce- dure. Slightly better fitting results were attained by con-

sidering acceptor reactions with the - and -triflate in- termediates as bimolecular processes. However, kinetic constants derived with the alternative mechanistic as- sumption, that is unimolecular, would still be consistent with the conclusion previously outlined (Figures S18-S19): the formation of the major -glycosylation product is rate- limited by the interconversion between - and -glycosyl triflates, in this case, even at roughly stoichiometric triflu- oroethanol concentrations. This behavior results from the peculiar reactivity of the -allosyl triflate intermediate whose substitution with the acceptor alcohol seems clearly favored over the one involving anionic triflate.

***Primary 13C-Kinetic Isotope Effect (KIE) analyses for the glucose and allose cases.-*** As a next step, to get fur- ther insights into the reaction mechanisms, the primary 13C-KIEs for both dominant products, the -glucoside and the -alloside formed with trifluoroethanol, were deter- mined employing the NMR method originally proposed by Singleton23 and later adapted by Crich10d for low tempera- ture chemical glycosylations. Individual values measured at three different reaction conversions, together with the corresponding average are represented in Table 2. It should be noted that according to the kinetic model con- sidered in Figures 4d and 7c, both 13C-KIE values could, to some extent, have contributions arising from both the triflate anomerization and the subsequent alcohol trap- ping, thus making an in depth analysis of these single val- ues not straightforward. Notwithstanding, they can still be employed for comparative purposes as similar reactions have been already analyzed by this method. Thus, for the glucose case the 13C-KIE value determined (1.012) lies significantly closer to the range expected for SN1-like sub- stitutions (1.00-1.01), rather than to concerted SN2 reac- tions (1.03-1.08). Comparatively, a 13C-KIE of 1.023 has been reported for the -glycosylation of the same triflate intermediate with isopropanol.10d According to these data, the replacement of isopropanol by a poorer nucleophile determines a shift in the reaction mechanism towards a more dissociative process, as proposed by Codée and Crich.10,11a-b

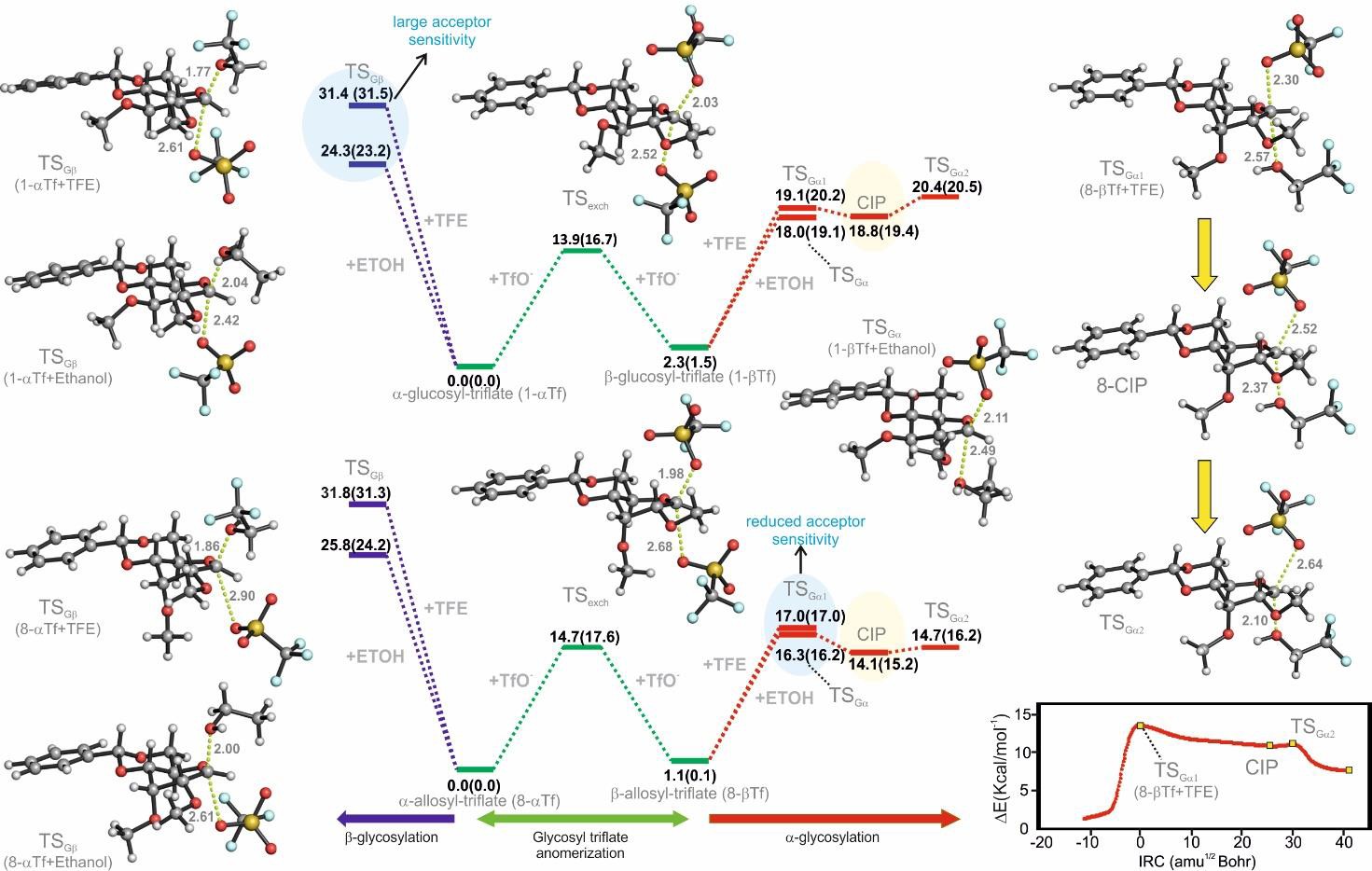
**Table 2.-** Experimentally determined primary 13C-KIEs. Obtained values for the -glucopyranoside **4**and the - allopyranoside **10**were measured at -65 oC (CHCl3) and - 80 oC (CH2Cl2), respectively, with three different reaction conversions. From them, the corresponding values at 25 oC were calculated.

|  |  |
| --- | --- |
| ***Conversion*** | ***4*** |
| 11% | 1.013 |
| 15% | 1.012 |
| 21% | 1.010 |
| Average | 1.012±0.002 |
| ***Conversion*** | ***10*** |
| 6% | 1.004 |
| 15% | 1.005 |
| 20% | 0.998 |
| Average | 1.002±0.004 |

Regarding the allose model, the obtained value (1.002) points to an even more dissociative process involving, most likely, the participation of a contact ion pair (-CIP), which could be explained by a combination of factors. First, the axially oriented methoxy group at position 3 could favor contact ion pair formation by stabilizing the positive charge located at the anomeric position via through-space polar interactions.24 And secondly, the large fraction of the

-allosyl triflate in equilibrium must also determine a higher population of the corresponding -CIP, the species presumably involved in the substitution process. Overall, the obtained results for both glycosylation processes sug- gest the participation of discrete short-lived oxocarbeni- um-like intermediates, structurally related with the corre- sponding parent -glycosyl triflates. However, despite the dissociative character attributed to the reactions involving such intermediates, our results seem to imply that the alcohol is still involved in a kinetically significant way, on the basis of the sensitivity exhibited by the reaction rates to both the nucleophilicity and the concentration of the acceptor.

***Quantum mechanical calculations.-*** With the aim of further dissecting the interplay between triflate anomeri- zation and the alcohol substitution processes we analyzed the ground/transition states involved by quantum me- chanical calculations (see Computational Details), consid- ering both ethanol and trifluoroethanol as acceptor alco- hols. Computed energies and geometries are represented in Figure 8. Some clear trends are apparent from these data: First, the formation of the -glycosides from the cor- responding -triflates via a direct inversion mechanism proceeds, in all cases, through high energy TSs (herein referred to as TSG; Figure 8, which are significantly more unfavored for the trifluoroethanol-involving reactions. Conversely, -glycosylation processes show lower activa- tion barriers and much reduced sensitivities to the nucleo- philic character of the alcohol, in agreement with the com- petition experiments reported above. Additionally, TSs involved in triflate anomerization and -glycosylations (named TSExch and TSGrespectively) display comparable stabilities. Indeed, for the allose case, a considerable devia- tion from the Curtin-Hammett scenario is correctly antici- pated, reflecting the balance between assisting and oppos- ing influences of the pyranose axial substituent on both processes. Certainly, while this methoxy group stabilizes TSGby means of a hydrogen bonding interaction with the incoming alcohol, it destabilizes TSExch through repulsive interactions with the anionic triflate nucleophile. This is in good agreement with the experiments herein reported, which show that the relative stability between TSGand TSExch is, in fact, even more tilted in favor of the former, with ΔG‡Gα ΔG‡Exc for glucose (Figure 4) and ΔG‡Gα ΔG‡Exc for allose (Figure 7). Of note, single-point energy calcula- tions with SMD(CHCl3)/M06-2X/6-311++G(2d,p) im- proved the results observed at the PCM(CHCl3)/M06- 2X/6-31G(d,p) level used for geometry optimizations and correctly reproduced the trend observed experimentally: triflate exchange is the rate-limiting step for allose, thus making the -glycosylation rate almost independent of the nature of the accepting alcohol within this range. It is im- portant to mention that the inversion of pyranose



**FIGURE 8**.- Relative stabilities for the transition states and intermediates involved in the anomeric substitution of glucosyl (up) and allosyl (down) triflates with ethanol and trifluoroethanol (employed notation is shown below), evaluated by quantum mechanics. Computed geometries for selected transition states and intermediates are also represented. The reaction coordinate calculated for the anomeric substitution of the -allosyl triflate with trifluoroethanol is shown at the bottom-right corner, together with the geometry of the pertaining TSs/intermediates along this path (above). Geometries and intrinsic reaction coordinates (IRC) were calculated with PCM(CHCl3)/M06-2X/6-31G(d,p). Relative free energies (ΔG and ΔG‡) are given in kcal/mol and intera- tomic distances in angstroms. Relative stabilities derived through single-point energy calculations at the SMD(CHCl3)/M06-2X/6- 311++G(2d,p)//PCM(CHCl3)/M06-2X/6-31G(d,p) level are shown in parentheses.

configuration at position 3, from D-gluco- to D-allo-, effec- tively diminishes the energy gap between - and - glycosyl triflates, as shown experimentally. However, a slower triflate anomerization is predicted for the allose case in both the →and →directions. This is only in partial accordancewith our experimental data, which re- vealed a faster →inversion for the -allosyl triflate.

Regarding the computed geometries for TSExch as well as TSGand TSGwith ethanol (Figures 8 and S20-S25), they can be broadly classified as loose (exploded) SN2 transi- tions states, similar to those previously described by Crich and Bennet for other anomeric substitutions.10,12 Interest- ingly, while -glycosyl triflates evolve through late TSs,characterized by larger distances between the anomer- ic carbon and the departing group, the corresponding - anomers progress through early TSs, with shorter distanc- es to the leaving triflate anion. This distinct behavior most probably reflects the operativity of the anomeric effect which renders the -anomers more stable. As expected, the loose character exhibited by the calculated TSs with ethanol is further exacerbated for the trifluoroethanol reactions. Thus, according to our theoretical calculations, the anomeric substitutions of the -glycosyl triflates with

this acceptor proceed with the concomitant formation of a close-ion pair (CIP), now identified as a broad minimum in the reaction coordinate (Figure 8), which is separated from both the starting -glycosyl triflate and the -glycosylation product by exceedingly low energy barriers. Of note, the allosyl CIP is around 2 kcal/mol more stable than the cor- responding glucosyl CIP, as previously hypothesized in light of the experimental results. Intrinsic reaction coordi- nate (IRC) calculations proved that very asynchronous but concerted reaction pathways operate for all anomerization and glycosylation reactions except for the α-glycosylations with trifluoroethanol, for which a stepwise inversion mechanism was consistently found (Figure S23). For glu- cose, this process would be rate-limited by the nucleophilic attack of the alcohol to the contact-ion-pair intermediate (TSG2) in agreement with a DN\*ANǂ mechanism. Indeed, the theoretical KIE calculated at 25 oC for TSG2 amounts to 1.0154, in line with the experimental value. On the contra- ry, for allose, hydrogen bonding of the alcohol to donor position 3 would lead to a preferential stabilization of TSG2 with respect to TSG1 and a DNǂ\*AN reaction is pre- dicted. However, in this case, the theoretical KIE, derived from TSG1 amounts to 1.0167, showing a larger deviation from the measured value. Most likely, the minute energy

differences between TSG1 and TSG2 predicted by the calcu- lations for allose (0.8 kcal/mol at the highest level) renders the distinction between DN\*ANǂ and DNǂ\*AN mechanism extremely difficult to pinpoint. Overall, the theoretical rendition of the glycosylation reaction presented herein manages to capture most of the key features experimental- ly observed for the processes herein described, and sup- ports the atypical mechanistic interpretation inferred from our model systems.

#### DISCUSSION

The obtained results highlight the mechanistic relevance of -glycosyl triflates in glycosylation processes, either as reactive intermediates or as reservoirs of even more un- stable cationic species, and show that the population and reactivity properties of each anomer together with their mutual exchange dynamics determine to a large extent the stereochemical outcome of the reaction. Regarding - triflate population, its influence is clearly illustrated by the distinct behavior exhibited by the glucosyl- and mannosyl- triflate mixtures in our competition experiments type ***c-II***: the reaction with ethanol yields -glycosides with nearly identical rates, while -product formation is around 10- fold faster for the glucose model, probably reflecting the increased fraction of -triflate available in this case. Ac- cordingly, this process is further accelerated for the allosyl donor, whose -triflate equilibrium population is noticea- bly much higher.

Regarding the intrinsic reactivity properties of the gly- cosyl triflate intermediates, our competitions type ***c-I*** re- veal some general trends which are common for the man- no-, gluco- and allo- donors assayed. Thus, the reaction mechanism leading to the -products display, in all cases, a significant sensitivity to the nucleophilic character of the acceptor, within the ethanol-trifluoroethanol range, while the opposite is true for the -stereomers. The simplest interpretation of these observations is that the former derivatives are generated through bimolecular SN2-like substitutions taking place upon the major, more stable - glycosyl triflate. On the contrary, -glycoside formation must involve the participation of more reactive, less dis- criminating intermediates, such as -glycosyl-triflates or even -glycosyl CIPs, which become especially relevant when poor acceptors are employed.

Despite the widespread interest on these latter chemical processes, a detailed picture of the underlying mechanism was still incomplete. With this idea in mind, we set out to dissect two representative examples of these reaction pathways. In the first instance, we focused our attention on the glycosylation of glucose derivative **1a** with trifluoro- ethanol, which renders a dominant retention -product from a seemingly exclusive -glycosyl triflate intermedi- ate. Our second model system was provided by allose do- nor **8a** and its reaction with the same acceptor. This choice is justified on the basis of chemical considerations, which pointed to an unusually large population of -triflate in- termediate for this particular hexopyranose. Our first ef- forts were oriented to confirming the presence and, in such case, quantifying the population of these reactive species in the activated reaction mixtures. For the glucose case this goal was achieved by resorting to 13C-labeled samples

which allowed us to detect a very minor equilibrium con- centration of the -triflate derivative, thereby defining the equilibrium constant and the free energy gap between both anomers. Regarding the allose donor, NMR experi- ments not only confirmed our predictions, revealing a remarkably large fraction of the corresponding -glycosyl triflate in solution, but also allowed the analysis of the anomerization process with unprecedented detail. Hence, equilibrium and kinetic constants were determined under a variety of solvent and temperature conditions. Notably, EXSY NMR experiments performed in the presence of in- creasing concentration of TBAOTf were consistent with a bimolecular anomerization mechanism.

With this information in hand, the time evolution of glu- cosyl- and allosyl triflates upon addition of increasing concentrations of trifluoroethanol was analyzed. The ob- tained results with both glucose and allose model systems draw a common scenario: the anomeric substitution of the

-glycosyl triflate with anionic triflate to yield the corre- sponding -anomer is, in all cases, significantly faster than the reaction with trifluoroethanol to produce the inverted

-glycoside. This observation is in agreement with the reported21b relative nucleophilic character of both acceptor species and partially explains the -stereoselectivity of both glycosylation processes. However, the more unstable

-triflate displays the opposite behavior, showing no pref- erence for any of them, as in the glucose case, or reacting even faster with the alcohol, as in the allose case. Several non-exclusive explanations could account for this latter observation: the nucleophilic attack of the anionic triflate through the -face of the -allosyl intermediate is hin- dered by a polar/steric repulsion with the axially oriented methoxyl substituent at the pyranose position 3, as sug- gested by the >20-fold drop in the calculated rate constant for this step, k, in comparison with the glucose case. Alternatively, the very same substituent may assist the nucleophilic attack of the neutral alcohol via an intermo- lecular hydrogen bond interaction, not available for the triflate anion, as supported by our theoretical analysis. According to this view, the hydrogen bonding capacity of the acceptor alcohol (especially that of poor acceptors) would drive the pre-formation of glycosyl-triflate/acceptor complexes which collapse to the final glycosylation prod- ucts upon departure of the anomeric leaving group, in line with a SNi contribution to the substitution mechanism re- cently proposed for 3-amino-3-deoxy-allose donors.25

Ultimately, the obtained results show that the analyzed glycosylations do not satisfy the Curtin-Hammett bounda- ry requirements for which triflate anomerization should be much faster than the alcohol substitution processes. This conclusion is visually illustrated by the preferential con- sumption of the -allosyl triflate over its -counterpart, which determines that the conversion rate of the -triflate intermediate into the major retention -glycoside product is defined by the →triflate anomerization. Such piece of experimental evidence links the formation of the - glycoside with the triflate exchange process, implying that the latter can become the rate-limiting step. Additionally, the obtained primary 13C-KIE values point toward very dissociative substitution processes involving oxocarbeni- um-like reactive species. Altogether, these data support a

-triflate intermediate acting as the exclusive source of - CIP, whose life-time must be too short to allow solvent equilibration.12a

#### CONCLUSIONS

Glycosylation reactions involving glycosyl triflate inter- mediates and weakly nucleophilic alcohols are known to proceed with increased or even complete -selectivity, presumably reflecting the participation of extremely reac- tive species, such as the corresponding -triflates or even glycosyl oxocarbenium ions, otherwise marginally popu- lated in the reaction medium. This evidence has guided the development of new synthetic strategies oriented to di- recting the stereochemistry of the newly formed glycosidic bonds.11b However, a detailed description of the mecha- nism underlying these processes was still missing. Herein, we have performed a thorough analysis of several para- digmatic and illustrative examples employing a combina- tion of experimental and theoretical chemical approaches that include synthetic chemistry, NMR, kinetic analysis and computational studies. Despite the highly dissociative character assigned to these processes, which probably involve a -CIP as the reacting donor species, the obtained results provide support for the key role of the -triflates as a cornerstone in -glycosylations. Therefore, the SN2-like anomerization of the preponderant -triflate represents an essential step which necessarily precedes glycosidic bond formation. Strikingly, under certain experimental circumstances, weak acceptor alcohols can indeed out- compete the triflate anion in the -triflate substitution, thus turning the glycosyl triflate exchange into the rate determining step. In our opinion, this behavior reflects the distinct properties of neutral and charged nucleophiles under the low polarity/low temperature conditions com- monly employed in glycosylations. Against common belief, and according to our data, only extraordinarily weak alco- hols (i.e. HFIP) react within Curtin-Hammett boundary conditions.

ASSOCIATED CONTENT

A detailed description of the experimental methods and synthetic protocols together with the characterization of products and intermediates. Figures S1-S26 with details of the NMR, reactivity experiments and QM calculations.

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‡AGS and LM-J are both first authors

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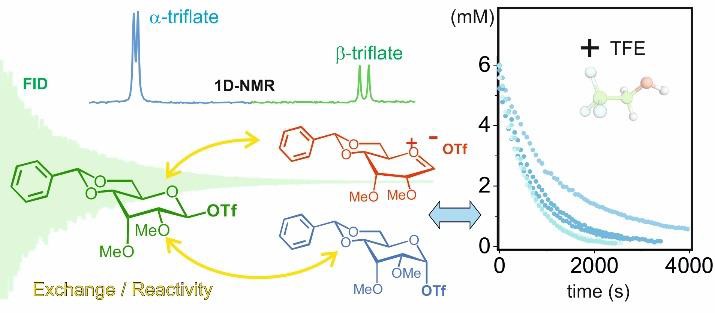
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