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Thermodynamic and kinetic considerations in the chemoselective O-acylation by mixed anhydrides. A semiempirical MO approach ☆

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Abstract—A simple methodology to achieve high chemoselective O-acylation of primary hydroxy groups, in the presence of secondary ones, was performed by means of the quick generation of a mixed anhydride using mild and inexpensive conditions. Steric and electronic factors are involved in this preference. As far as the geometries are concerned, semiempirical calculations were carried out in order to determine the nature of the contribution to the thermodynamics and kinetics. From a qualitative point of view, it was found that the thermodynamics are sugar dependent whereas the kinetics are mixed anhydride dependent. These conclusions fit quite well with the experimental results allowing the use of semiempirical MO calculations as a tool for modulating the selectivity ratio for this process since different systems may be modeled in the same way.

The selective protection of functional groups is one of the most critical aspects of many synthetic strategies. Satisfactory chemoselectivity is often achieved by taking advantage of electronic differences of the functional groups or of their distinct steric environments. Since the latter factors constitute usually the most important contribution for the selectivity in organic reactions, many strategies employing either hindered substrates or bulky reagents (or both) have been developed.[1] However, it is very difficult to introduce small protecting groups with acceptable selectivity through direct and inexpensive methods because reagents involved in the protecting process (as acetyl chloride in sugar acetylation) readily react with all the unprotected positions, having no way to discriminate them on the basis of steric and electronic factors, leading to mixtures. This is the reason why per-acylated sugars are common starting materials in carbohydrate chemistry.[2]

Anhydrides are in many cases reactive enough to be employed instead of acyl halides, which usually react using well controlled conditions.[3] Moreover, anhydrides are readily available, versatile and economical reagents. For instance, mixed anhydrides synthesized with sodium [^{13}C] acetate and pivaloyl chloride, have been employed particularly for the synthesis of labelled compounds.[4] Among other different strategies leading to the title compounds it is worth mentioning the reaction of thallium carboxylates with acyl chlorides,[5] of arenediazonium salts and sodium carboxylates under palladium catalysis,[6] the reaction between the corresponding free acid and ketenes,[7] or from the free acid and acyl chloride in a solid-phase co-polymer.[8] Related to mixed anhydrides, different interesting studies have been carried out, for example, their stabilization by the triethylboroxin complex formation,[9a] photochemical cleavage reactions,[9b] as well as their use in the electroreduction of benzylic and allylic halides to afford ketones.[9c] Although numerous reports on the synthetic utility of anhydrides have been reported, only very limited information is available concerning their reactivity as a function of their structure.[10]

This work describes the use of mixed anhydrides as a source of different acyl protecting groups (acetyl and benzoyl), the acylation process being chemoselective on account of structural parameters.

Thus, mono-saccharides 1,2-*O*-isopropylidene-α-D-*xylo*- (**1**), 3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*gluco*- (**2**), 1-*O*-benzyl-2,3-*O*-isopropylidene-α-L-*sorbo*- (**3**) and 2,3-*O*-isopropylidene-α-L-*sorbo*-furanose (**4**), have been selected as starting materials in order to study the scope

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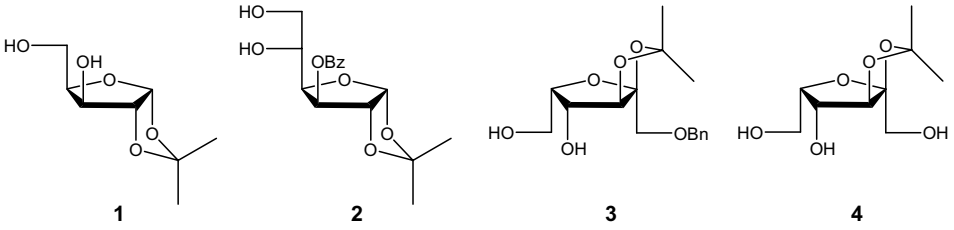

Figure 1. Compounds used as starting materials.

of the selective 5-(6-) O-acetylation and 5-(6-) O-benzoylation. Hence, compound **2** is a 1,2-diol, whereas compounds **1**, **3** are 1,3-diols. Moreover, the 1,3-diol **4** has an additional more hindered primary hydroxy group (Fig. 1).

Acylations were performed by reaction of the corresponding sugars (**1**–**4**) with a solution of either acetic pivalic (for acetylation) or benzoic pivalic (for benzoylation) mixed anhydride, which were generated in situ.[11] Both acetylation and benzoylation took place in a highly chemoselective way, since acylation of the secondary hydroxyl group was negligible in all cases, affording the corresponding 5-*O*-acyl or 6-*O*-acyl derivatives, depending on the sugar (Fig. 2).

It is worth mentioning that compound **4** reacts to give **11** as the major product. In this case, small amounts of 1-*O*-acetyl and 1,6-di-*O*-acetyl derivatives were observed. Actually, it was found in all cases that the concurrent reaction was the protection of the primary hydroxy functionality by the pivaloyl moiety. As expected, this undesired reaction was more important for benzoylation (for which chemoselectivity decreased) and was directly responsible for the moderate yields achieved for the major products. This data is summarized in Table 1.

We can explain these results on the basis of a double steric induction for the acyl-transfer reaction: first, the more accessible and reactive primary hydroxyl group and second, the more accessible acetyl or benzoyl group in the mixed anhydride (Fig. 3). Obviously, the larger size of the benzoyl group with respect to the acetyl one leads to a lack of selectivity in the acylation process.

The computational study was performed by means of AM1 and PM3 semiempirical MO calculations, both methods implemented in the Hyperchem 7.5 package.[12]

Table 1. Yields afforded in the acylation reaction

Compounds	1	2	3	4
5-(6-)-*O*-Acetyl (%Yield)	**5** (77)	**7** (75)	**9** (76)	**11** (63)
5-(6-)-*O*-Benzoyl (%Yield)	**6** (68)	**8** (66)	**10** (70)	—[a]

[a] Complex mixture.

Calculations were carried out as close-shell type (RHF) using the Polak–Ribiere optimization algorithm, except for transition states for which eigenvector-following algorithm was employed. Convergence limits for all the evaluated systems were fixed at 0.01 kcal $Å^{-1}$ mol^{-1} (RMS gradient) for the geometry optimization process and 0.001 kcal mol^{-1} for the iterative SCF calculation. Geometries for the starting molecules were modeled before by molecular mechanics (Amber 99 force field).

In order to evaluate the thermodynamics of the different processes, geometry optimization calculations (ground state) were carried out by choosing the simplest 1,2- and 1,3-diols, namely compounds **1** and **2**, since these reactions seems to be similar for the other derivatives. In addition, both primary and secondary hydroxy group mono-substituted derivatives have also been considered for comparison, including the undesired pivaloylation reaction (Tables 2 and 3).

From this data, several interesting conclusions can be drawn. Firstly, in the case of the reactions on the primary hydroxy group (Table 2), all the processes are thermodynamically favored and only slight differences can be observed along the acetylation–benzoylation–pivaloylation series, both methods AM1 and PM3 being almost coincident. In addition, for the 1,2-diol **2** these processes are between 1.7 and 2.7 kcal mol^{-1} less favoured than they are for compound **1**. This fact can be explained considering that the entering group in the

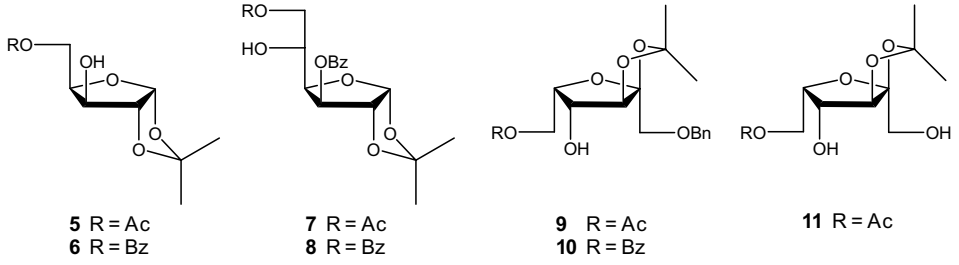

Figure 2. Main acylation products.

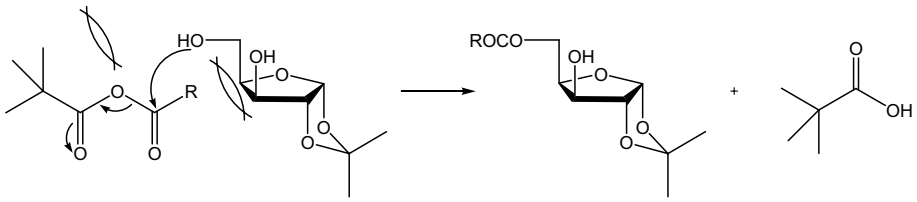

Figure 3. The schematic acyl-transfer process.

Table 2. Acetylation, benzoylation and pivaloylation on the *primary* hydroxy group for compounds **1** and **2**

Reaction	Substrate	AM1[a]	PM3[a]
Acetylation	**1**	−9.58	−8.86
	2	−7.84	−6.23
Benzoylation	**1**	−9.84	−7.99
	2	−7.71	−6.26
Pivaloylation in the acetylation	**1**	−9.26	−8.58
	2	−7.53	−5.88
Pivaloylation in the benzoylation	**1**	−9.67	−9.00
	2	−7.94	−6.30

[a] Energy values in kcal mol^{-1}. See the supplementary material section for further details.

Table 3. Acetylation, benzoylation and pivaloylation on the *secondary* hydroxy group for compounds **1** and **2**

Reaction	Substrate	AM1[a]	PM3[a]
Acetylation	**1**	−8.06	−6.52
	2	−6.10	−1.87
Benzoylation	**1**	−8.04	−6.73
	2	−6.40	−2.13
Pivaloylation in the acetylation	**1**	−7.95	−6.31
	2	−6.01	−1.65
Pivaloylation in the benzoylation	**1**	−8.36	−6.73
	2	−6.26	−2.07

[a] Energy values in kcal mol^{-1}. See the supplementary material section for further details.

molecule exhibits a greater hindrance when the hydroxy group is placed closer (that is, for 1,2-diols). Note also that, as expected, the pivaloylation process is slightly more favored when a benzoylation reaction is carried out because of the greater hindrance of the benzoyl group with respect to the acetyl group.

Then, in the case of the reactions on the secondary hydroxy group (Table 3), the same tendency can be seen for the energies, which only vary slightly along the series, showing again that pivaloylation is slightly more favored when benzoylation is carried out. However, now the energy differences exhibited between AM1 and PM3 for the thermodynamically less stable substituted 1,2-diol are too large (4.0–4.5 kcal mol^{-1}), although is the same difference (4.5–5 kcal mol^{-1}) that PM3 itself shows between the reactions on **1** and **2**. This clearly means that PM3 takes into account factors that AM1 simply ignores, that is to say, AM1 overestimates the stability of these compounds. On the other hand, PM3 shows frequently the opposite tendency. Such a behavior is widely known for these methods.[13] Considering that in this case compound **2** has two neighboring secondary substituted hydroxy groups (at 3 and 5 positions), the results afforded by PM3 become quite reasonable on account of steric factors.

Finally, due to the fact that only very slight energy differences can be observed along the series when varying the size of substituents (acetyl–benzoyl–pivaloyl), and that energy differences come only from different substituted positions on the sugar, it can be concluded that the thermodynamics take mainly into account the environment of the sugar, that is to say, it is sugar-sterically determined. This is the origin of the high chemo-selectivity observed.

On the other hand, the steric environment at the mixed anhydride (the acylating agent) has been shown to influence the regioselectivity observed since the major products correspond to a transfer of the smaller component of the mixed anhydride to the sugar skeleton. Since the different size of these substituents is not a critical factor in the energy of the final products, the environment at the mixed anhydride must be the determinant step in the reaction, controlling kinetically the preferred acetyl or benzoyl addition towards the pivaloylation process. Therefore, for these reactions, kinetics is mainly mixed anhydride-sterically determined. In order to evaluate this influence, it was necessary to establish the corresponding transition states.

These calculations aimed at transition states with forms that could be considered as six-membered half chair-like intermediates, where the hydroxy group participates doubly in a simultaneous process: the hydrogen atom is being transferred to the most distant carbonyl on the mixed anhydride while acylation takes place over the oxygen (Fig. 4).

A complete chemoselectivity between primary and secondary hydroxy groups is expected since the complex is too voluminous. However, it is possible to have transition states where either the acetyl (or benzoyl) or the pivaloyl moieties are the reaction targets, the latter resulting in the observed side reaction. Both possibilities have been studied for acetic pivalic and benzoic pivalic mixed anhydrides in the selective 5-O-acylation of compound **1** (Fig. 5).

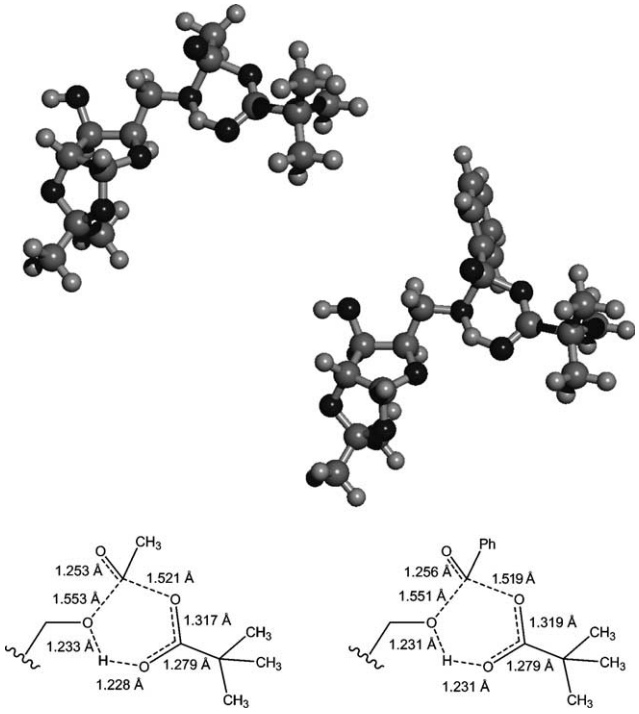

Figure 4. AM1 transition-state geometrics for the acetylation (left) and benzoylation (right) of **1** with the corresponding mixed anhydrides.

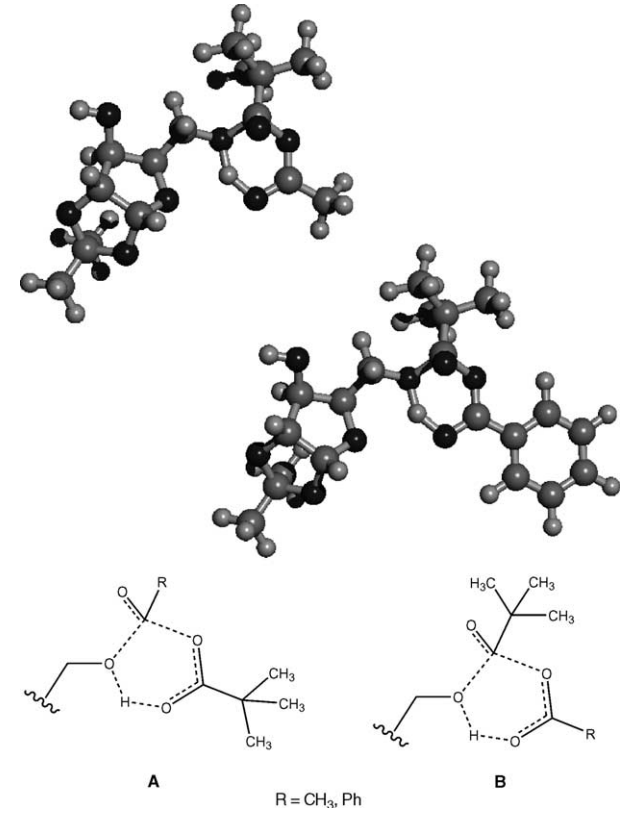

Figure 5. Above, the two **B** intermediates (acetyl and benzoyl) leading to pivaloylation (AM1). Below, a schematic representation of the transition states leading to the major products (**A**) and the undesired pivaloylation reaction (**B**).

Table 4. AM1 and PM3 energy differences between **A**–**B** states for the acylation process (kcal mol^{-1})

	AM1 **A**–**B** energy	PM3 **A**–**B** energy
Acetylation	−2.97	−1.31
Benzoylation	−1.04	+0.31

The energy difference between the **A** and **B** states is a qualitative measure of the kinetic preference for the smaller substituents. The results afforded fit quite well with the selectivity encountered experimentally (Table 4).

These values show that the AM1 method always considers the **A** states as the lowest energy complexes, the benzoylation being less favorable as expected. In contrast, PM3 calculations place pivaloylation (**B** state) only a little more favorably than benzoylation.

In summary, we have presented a new method for selective protection of primary hydroxy groups in sugar derivatives using an extremely simple protocol. This selectivity is based on the fact that introducing a sterically hindered component (namely pivalic acid) in the mixed anhydride leads to a bulky structure that reacts with the less hindered group in the substrate transferring their smaller component. This concept of double induction can be considered separately in both thermodynamic and kinetic factors. Semiempirical MO calculations have been carried out in order to determine the nature of each contribution, finding that the thermodynamics are not affected by the different size of the substituents but the specific environment in the sugar moiety (sugar control). Conversely, the kinetics determine the type of substituent that will be introduced (mixed anhydride control). These results indicate the fact that a wide number of different mixed anhydrides can be used in the same manner, being able to modulate both chemo- and regioselectivity.

Supplementary material

Energies and Cartesian coordinates of all the calculated structures are available.

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11. Pivaloyl chloride (1 mmol) was added to dry CH_2Cl_2 (20 mL). To this solution was added sodium acetate or sodium benzoate (10 mmol). The suspension was placed into an ultrasound bath and after 5 min, a solution of the corresponding sugar (1 mmol) in CH_2Cl_2 (10 mL) was added. After the disappearance of the starting material the mixture was washed with water (15 mL), the organic extract was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography to afford the corresponding acylated products.
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