Organotin-Mediated Monoacylation of Diols with Reversed Chemoselectivity. Mechanism and Selectivity[1]

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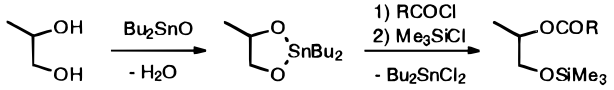
The monoesterification of unsymmetrically substituted diols, which occurs at the most substituted hydroxyl when activation of the substrate is achieved through its dibutylstannylene acetal, has been investigated to ascertain the origin of the unusual reversal of chemoselectivity. A mechanism in which the dibutylstannylene acetal plays the double role of reagent and catalyst has been established, which accounts for the reactivity, selectivity, and product distribution of the reaction. The reaction pathway involves three subsequent steps, namely, (a) esterification, (b) intra- and intermolecular transesterification, and (c) quench; interplay between kinetic and thermodynamic control over the three steps is responsible for the observed product distribution. The knowledge of the reaction mechanism allows for adjustment of experimental conditions to achieve optimum selectivity, which can be >99% with the appropriate choice of reagents. The stannylation procedure converts hydroxyls into functional groups highly chemoselective toward acyl reagents, but inert toward sulfonyl halides and alkylating reagents. The reactivity of the Sn−O bond has been found to decrease with decreasing the electronegativity of ligands on tin, while halide ligands appear to be essential for reversal of chemoselectivity. A structure has been proposed for the catalytic species, in which complexation of the stannyl monoester intermediates with the starting dioxastannolane reagent activates the stannylated oxygen toward addition to the carbonyl and at the same time accounts for the steric hindrance that biases the intramolecular transesterification equilibrium toward the thermodynamically most stable monoester of the most substituted hydroxyl.

Introduction

Selective manipulation of diols and polyols is a central matter in synthetic organic chemistry,[2] particularly in the area of carbohydrates and polyhydroxylated compounds, where preparative procedures typically have to cope with repeated protection/deprotection steps.[3] Selective activation of hydroxyl groups by the stannylation procedure has become an established practice to efficiently achieve the target,[4] because of the easy preparation of the stannyl intermediates, their simple usage, and the good yields and selectivities obtained.

In this context, following a preliminary experimental observation,[5] a few years ago we developed a synthetic method that allows for the selective esterification of unsymmetrical diols at the *most substituted hydroxyl*,[6] that is, with reversal of chemoselectivity with respect to the natural reactivity of hydroxyl groups (Scheme 1). The described method[7] provides easy access to complementary products to those obtained by standard literature procedures, normally affording monoesters of the least substituted hydroxyl. Besides the good to excellent selectivities, a further aspect of interest of this method is that hindered monoesters can be prepared, with some remarkable achievements such as the esterification at the tertiary hydroxyl of a tertiary−primary diol and the secondary pivalate of a secondary−primary diol.[6]

Scheme 1



The interest in synthetic potentials and mechanistic aspects of this method have stimulated an investigation of the origin of such an unusual reversal of chemoselectivity, in the belief that the elucidation of the mechanism would open the way to full exploitation of the reaction. The investigation was based on previous findings on the organotin-mediated monoesterification of ethylene glycol with acyl chlorides,[8] for which a three-step reaction scheme had been established (Scheme 2). In the first step (A), an irreversible esterification of the dibutylstannylene acetal of ethylene glycol with 1 equiv of acyl chloride affords a stannyl monoester. The high monoesterification selectivity is due to a substantial deactivation of the second Sn−O bond toward further esterification by the presence of the chloride ligand on tin (*vide infra*). In the second step (B), an intermolecular transesterification reaction produces the diester from the stannyl monoester. Although the equilibrium favors the formation of the diester, the reaction is sufficiently slow not to interfere with the completion of the subsequent quench step (C) with an appropriate destannylating reagent, which af-

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1996.

(1) Group 14 Organometallic Reagents. 12. For part 11, see: Roelens, S.; Dalla Cort, A.; Mandolini, L. *J. Org. Chem.* **1992**, *57*, 1472.

(2) (a) Wilkinson, S. G. In *Comprehensive Organic Chemistry*; Pergamon Press: New York, 1979; Vol. 1, p 681. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991.

(3) *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolfrom, M. L., Eds.; Academic Press: San Diego, 1963; Vol. 2.

(4) (a) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643. (b) Pereyre, M.; Quintard, J. P.; Rahm, A. In *Tin in Organic Synthesis*; Butterworths: London, 1987; p 261.

(5) Ricci, A.; Roelens, S.; Vannucchi, A. *J. Chem. Soc., Chem. Commun.* **1985**, 1457.

(6) Reginato, G.; Ricci, A.; Roelens, S.; Scapecchi, S. *J. Org. Chem.* **1990**, *55*, 5132.

(7) For recent alternative methods, see: Bailey, W. F.; Zarcone, L. M. J.; Rivera, A. D. *J. Org. Chem.* **1995**, *60*, 2532 and references cited therein.

(8) Roelens, S. *J. Chem. Soc., Perkin Trans 2* **1988**, 2105.

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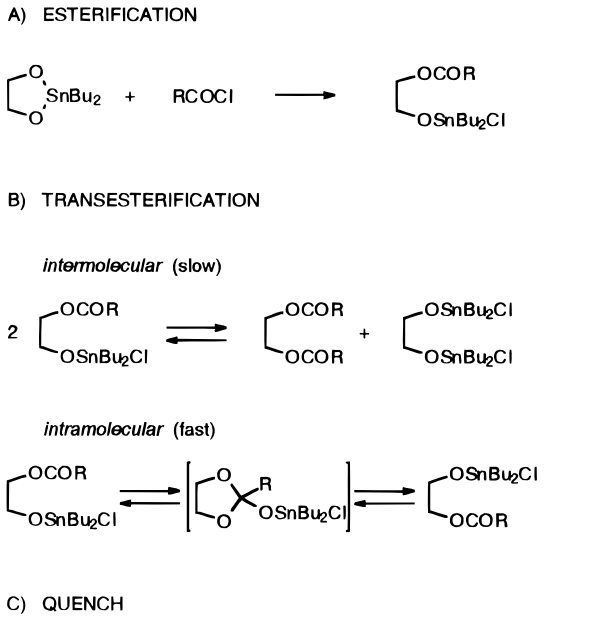
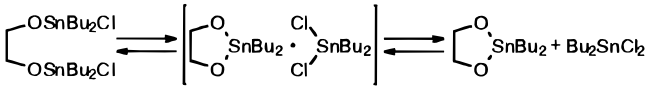
Scheme 2



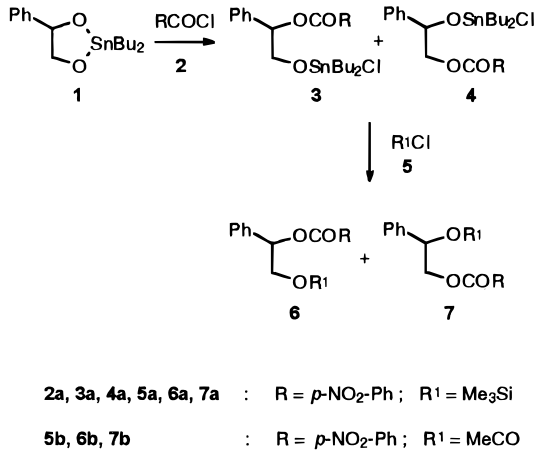
Scheme 3



fords a stable, isolable monoester.[9] The described transesterification reaction can also occur intramolecularly (Scheme 2, B), giving rise to a virtual equilibrium that scrambles the acyl group between the oxygen atoms of the diol through a five-membered tetrahedral intermediate. This reaction, taking advantage of the large intramolecularity factors that favor five-membered rings,[10] experiences a substantial rate increase with respect to its intermolecular counterpart, so that the equilibrium is established before quench can take place. Convincing evidence for the existence of the intramolecular equilibrium was provided by coalescence of the CH_2OSn and CH_2OCOR signals in the ^{1}H NMR spectra.[8] In this scheme, a key role is played by the bis-stannylated diol formed in step B as a side product of the diester. This species has been shown to take part in a fast equilibrium in which the starting dioxastannolane is regenerated, by elimination of 1 equiv of dibutyltin dichloride (Scheme 3).[11]

On this basis, the investigation of the reversal of chemoselectivity translates into marking one of the two equivalent positions of ethylene glycol, which has been achieved by placing a substituent on one carbon of the dioxastannolane ring and monitoring the steps and the intermediates that lead to the observed product distribution. It should be noted that *regioselectivity* (preference for the ester of the "labeled" oxygen) and *chemoselectivity* (preference for the ester of the most substituted hydroxyl), *i.e.*, chemical and positional selectivities, are superimposed features for this reaction.

Scheme 4



2a, 3a, 4a, 5a, 6a, 7a : R = *p*-NO_2-Ph ; R^1 = Me_3Si

5b, 6b, 7b : R = *p*-NO_2-Ph ; R^1 = MeCO

Results and Discussion

Because of the excellent selectivities observed,[6] 1-phenyl-1,2-ethanediol was selected as a "labeled" substrate and converted into the corresponding dibutylstannylene acetal, and the investigation was carried out using appropriate acylating and quenching reagents. Selective monoesterification was performed according to the previously reported general procedure.[6] Crystallized 4-phenyl-2,2-dibutyl-1,3,2-dioxastannolane (**1**), prepared from the diol and Bu_2SnO by azeotropic dehydration, was allowed to react with 1 equiv of the selected acyl chloride **2** in $CDCl_3$ solution at room temperature, and the formation of the isomeric stannyl monoesters **3** and **4** was followed by ^{1}H NMR (Scheme 4). All the experiments were run under comparable concentrations of substrate (0.3 M ca.). Subsequent treatment with a second equivalent of the appropriate acyl or silyl chloride **5** quenched the reaction, affording the isomeric mixed diesters or the silyl monoesters **6** and **7** (Scheme 4). The final mixtures were quantitatively analyzed by ^{1}H NMR in the reaction medium without further manipulation.

Selectivity. The attention was focused on the regioisomeric distribution of monoesters, neglecting the monoselectivity of the reaction, which was analogous to that observed for ethylene glycol.[12] Reaction of **1** with 1.2 equiv of *p*-nitrobenzoyl chloride (**2a**) gave an approximately 2:1 mixture of secondary/primary (**3a**/**4a**) stannyl monoesters. As with ethylene glycol, broadening of lines in the ^{1}H NMR spectra revealed chemical exchange phenomena involving the stannyl monoesters. The mixture was quenched with a slight excess of Me_3SiCl (**5a**) at room temperature, monitoring the formation of silyl monoesters **6a** and **7a** *vs* time by ^{1}H NMR (Figure 1). It is clearly observed that **3a** and **4a** were converted in 15 min ca. into a 22:1 mixture of **6a** and **7a** (Table 1, entry 2), indicating that extensive redistribution of regioisomers had taken place during quench. Corresponding hydroxy esters **3*** and **4***, which where caused by hydrolytic destannylation and were present in the mixture in their "natural" distribution, *i.e.*, primary ester predominant over the secondary, do not interfere with quench, remaining unaffected in the time required for quench to be complete. Similarly, a mixture of **3a** and

(9) Hydroxy esters of 1,2-diols are known to isomerize. See, for example: (a) Cohen, T.; Dughi, M.; Notaro, V. A.; Pinkus, G. *J. Org. Chem.* **1962**, *27*, 814.

(10) Mandolini, L. In *Advances in Physical Organic Chemistry*; Academic Press: London, 1986; Vol. 22, p 1.

(11) Roelens, S. *J. Chem. Soc., Perkin Trans 2* **1988**, 1617.

(12) It was noted, however, that mixing effects in concentrated solution could significantly alter the selectivity of monoesterification, but not the regioisomeric distribution. This behavior indicates local concentration phenomena occurring in the fast esterification step (A), as supported by incresing sensitivity to mixing effects with increasing the electrophilic reactivity of the acyl chloride (acetyl > *p*-NO_2-benzoyl > *p*-MeO-benzoyl).

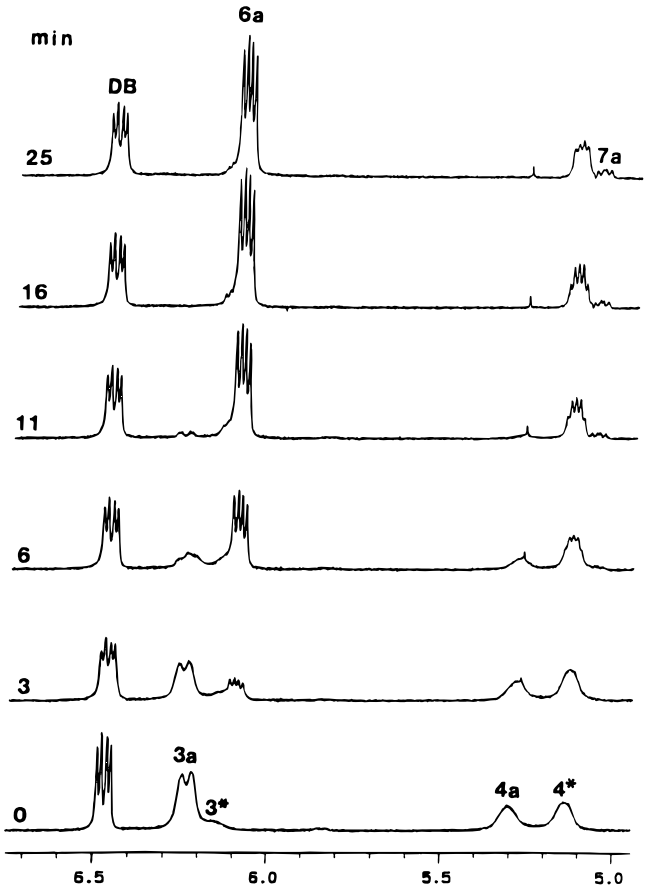


Figure 1. Quench of a mixture of stannyl monoesters **3a** and **4a** with **5a** at room temperature, monitored by ^{1}H NMR *vs* time. Only the PhC*H*O region is shown. **DB**: 1-phenyl-1,2-ethanediol bis(*p*-nitrobenzoate).

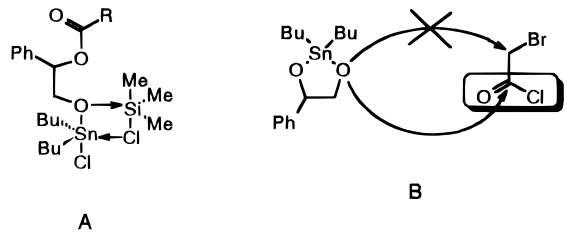
Table 1. Regioisomer Distribution in the Acylation of 1-Phenyl-1,2-ethanediol[a]

entry	RCOX	**3**:**4**	R^1Cl	**6**:**7**
1	*p*-NO_2-BzCl	3:1	AcCl	10:1
2	*p*-NO_2-BzCl	2:1	TMSCl	22:1
3	*p*-NO_2-BzCl	2:1	TMSCl (5 equiv)	7:1
4	*p*-NO_2-BzCl	3:1	*p*-MeO-BzCl	14:1[b]
5	(*p*-NO_2-BzCl + *p*-MeO-BzCl)[c]			7(NO_2):1(MeO)
6	BzBr	2:1	TMSCl	16:1
7	AcCl	4:1	*p*-NO_2-BzCl	>99:1
8	Br-AcCl	3:1	*p*-NO_2-BzCl	99:1

[a] All reaction were run at rt in $CDCl_3$, 0.3 M in substrate **1**. [b] Determined by ^{13}C NMR. [c] Pre-mixed reagents.

4a, quenched with an excess of acetyl chloride (**5b**), showed complete reaction at the first check after 3 min and afforded the mixed diesters **6b** and **7b** in a 10:1 ratio (Table 1, entry 1). Quenching experiments showed a reorganization, favoring products acylated on the secondary hydroxyl, that was more extensive the slower the quench. This evidence suggested that selectivity could, in principle, be modulated, up to complete monoacylation of the secondary hydroxyl, by appropriately tuning the reactivity of the acylating and the quenching reagents. Results obtained with a variety of reagents are reported in Table 1 and show that a very high level of selectivity can indeed be obtained. While distribution of the stannyl monoesters varied within a narrow range (2−4:1), that of quenched regioisomers spanned a much broader range, with secondary esters prevailing in all cases. Highest selectivities were obtained by quenching acylation mixtures of aliphatic acyl chlorides with *p*-nitrobenzoyl chloride, *i.e.*, for the largest reactivity difference between the acylating and the quenching reagents (Table 1, entries 7 and 8). An interesting result was obtained when **1** was treated with 2 equiv of a 1:1 mixture of *p*-nitro and *p*-methoxybenzoyl chlorides, *i.e.*, with pre-mixed "acylating" and "quenching" reagents (Table 1, entry 5). Selectivity is still observed, giving the secondary *p*-nitrobenzoate in a 7:1 ratio. Since for the two benzoyl chlorides reactivity is essentially determined by electronic effects, the most electrophilic acyl chloride behaves as the acylating reagent and reorganization takes place during quench carried out by the least reactive acyl chloride.

Scheme 5



In striking contrast to the generally high reactivity of stannoxane reagents toward carboxyl halides, the stannyl monoesters were unexpectedly inert toward other quenchers. For example, no evidence of reaction was obtained after 16 h at room temperature when a mixture **3a** and **4a** was treated with methanesulfonyl chloride. Even the extremely powerful methylating reagent methyl trifluoromethanesulfonate failed to quench the stannyl ester mixture. Such remarkable chemoselectivity suggested that these stannoxane reagents may be confined to react through an addition−elimination mechanism. Silyldestannylation carried out by **5a** is only apparently an exception, since it likely proceeds itself through an addition−elimination mechanism, involving a five-coordinate silicon center (Scheme 5A).[13] This hypothesis was tested by reacting **1** with bromoacetyl chloride, a reagent in which the two activated electrophilic centers would react through different mechanisms. Acylation products were observed *exclusively*, demonstrating complete lack of competition between acylation and alkylation (Scheme 5, B).

Esterification was further investigated with various reagents. Acetylation of **1** was attempted using an activated ester, *p*-nitrophenyl acetate, which turned out to be a far more sluggish acylating agent than acyl chlorides. Under similar conditions (0.2 M in $CDCl_3$, rt), it took hours to react appreciably, while reaction with acetyl chloride was complete right after mixing. Furthermore, monoesters were only 10% of the acylation mixture, exhibiting a secondary/primary ratio of 0.36:1. Quench with **2a** was fast, but preferentially gave the primary acetate (secondary/primary = 0.22:1). Acylation with benzoyl bromide (Table 1, entry 6) did not show any appreciable reactivity difference when compared to acylation with **2a**, except for a somewhat slower quench with **5a**, which was complete in 2 h under analogous conditions. Reaction of **1** with acetic anhydride (0.3 M in $CDCl_3$, rt) was complete at the first check after 6 min, but only 30% of the reaction mixture consisted of stannyl mono esters, predominantly the primary acetate (second-

(13) (a) Corriu, R. J. P.; Guerin, C.; Moreau, J. J. E. In *The Chemistry of Functional Groups: The Chemistry of Organic Silicon Compounds, Part 1*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1989; p 305. (b) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371.

ary/primary = 0.6:1). Quench with **5a** was complete right after mixing, but gave only trace amounts of the secondary acetate. Comparative analysis of data lead to the conclusion that the reactivity of the Sn−O bond, which decreases in the order O−Sn−OR > O−Sn−OAc, O−Sn−O(*p*−NO_2−Ph) > O−Sn−Cl > O−Sn−Br, can be appropriately explained in terms of electronegativity of ligands on tin. Such electronegativity/reactivity order accounts for the preferential formation of monoesters, due to the *deactivation* of the second Sn-O bond with respect to the first induced by the approach of a less electronegative Cl ligand. By the same argument, the larger electronegativity of the Cl compared to the S ligands is expected to induce a substantial *activation* of the second Sn−S bond when dithiastannanes are reacted with acyl chlorides, thus favoring diesterification. Such has indeed been shown to be the case in the acetylation of 2,2-dibutyl-1,3,2-dithiastannolane with acetyl chloride,[14] in which exclusive formation of the diester was observed, caused by a large increase of reactivity of the second Sn−S bond after the esterification of the first. However, even if the reactivity of stannoxane reagents can be accounted for, the need for halide ligands, which seems to be a requirement for chemoselectivity reversal, is still difficult to explain.

In conclusion, the stannylation procedure chemoselectively activates hydroxyls toward the acyl group and, in general, toward groups capable of reacting through an addition−elimination mechanism. Stannoxanes are easily silylated and esterified and they exhibit a marked preference toward acyl halides and anhydrides when compared to esters but are largely inert toward sulfonyl halides, alkylating reagents, and, most likely, other electrophiles which are unable to give addition−elimination reactions. In the monoesterification of diols, the presence of halide ligands on tin appears to be a prerequisite for reversal of chemoselectivity.

Mechanism. To gain an insight into the observed dynamic processes, a mixture obtained by reacting **1** with 1.2 equiv of **2a** was submitted to variable temperature experiments. An excess of acyl chloride was employed to provide an amount of diester useful as internal reference and to ensure complete consumption of the starting dioxastannolane **1**. Dynamic phenomena were conveniently monitored through the PhC*H* signals, which gave well-resolved resonances in a clean region of the ^{1}H NMR spectrum for all the species involved. Surprisingly, no tendency toward coalescence was observed between signals of **3a** and **4a** in the temperature range from −44 to 57 °C (Figure 2). Coalescence was instead observed in the higher temperature range between signals of **3a** and **4a** and those of the corresponding hydroxy esters **3**** and **4****, originating from destannylation caused by adventitious hydrolysis. On the other hand, a dramatic variation of the **3a**/**4a** ratio with temperature was evident, rising to 19:1 at −44 °C and falling to 0.8:1 at 57 °C. Although lack of coalescence was apparently in contrast, the full reversibility of the process unambiguously demonstrated that the stannylesters were involved in a fast exchange equilibrium with each other. It is noteworthy that while at low temperature the secondary monoester is strongly favored over the primary, at high temperature such preference vanishes. Thus, the bulky stannyl group preferentially resides on the less hindered primary oxygen at low temperature, but this constraint

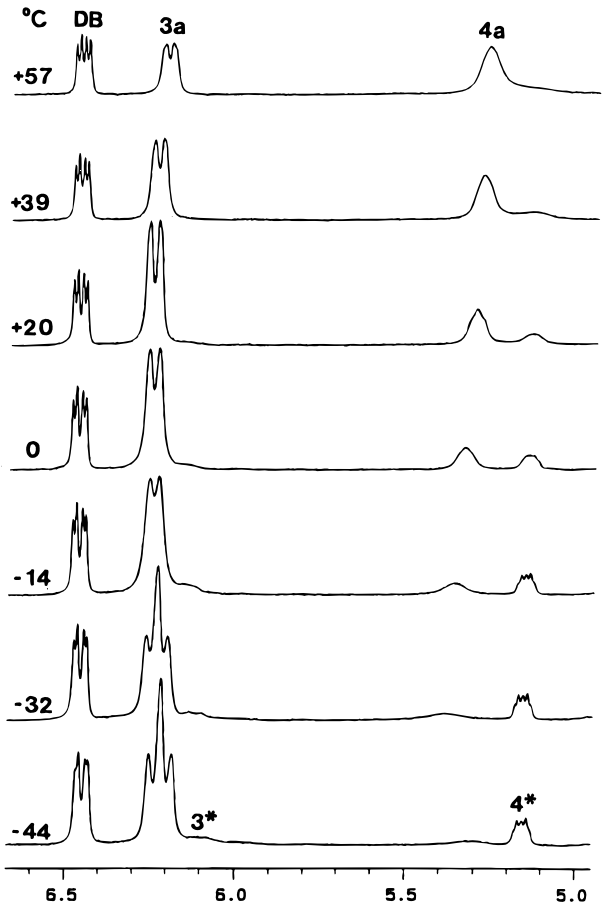


Figure 2. ^{1}H NMR spectra of a mixture of **3a** and **4a** at various temperatures. Only the PhC*H*O region is shown. **DB**: 1-phenyl-1,2-ethanediol bis(*p*-nitrobenzoate).

is progressively lost the higher the temperature. Such preference is reasonably steric in origin; a support is provided by the marked insensitivity of the **3a**/**4a** ratio to significant variation in electronic demand of the acyl group (Table 1).

It is relevant to stress here that this is the picture revealed *in the absence of dioxastannolane* **1**. The influence of the latter was investigated by adding **2a** to **1** in subsequent portions, up to 1.2 equiv, and following the stepwise formation of the intermediates at room temperature. Inspection of the resulting spectra in reverse order shows the effect corresponding to the addition of incresing amounts of **1** to the mixture of stannyl monoesters. In Figure 3, the spectra for various **1**/(**3a** + **4a**) ratios are reported, ranging from the absence to a 10-fold excess of **1**. Coalescence of signals is unambiguously observed, proving that **1** exerts the role of increasing the rate of exchange between **3a** and **4a**. On the contrary, hydroxy esters **3*** and **4*** are not significantly affected by increasing amounts of **1**. It can be noted that the **3a**/**4a** ratio is substantially insensitive to variable excess of **1**. Thus, only the rate of exchange is affected by the latter, not the equilibrium position, so the dioxastannolane behaves as a true catalyst for the transesterification reaction. Unexpectedly, when a mixture of **1**, **3a**, and **4a**, appropriately prepared at such a ratio of reagents as to be at coalescence of signals at room temperature, was submitted to variable temperature experiments divergence of signals for **3a** and **4a** was observed with increasing temperature (Figure 4), as would be expected for a decreasing rate of exchange. A complex and not easily interpretable pattern of process

(14) Dalla Cort, A.; Mandolini, L.; Roelens, S. *J. Org. Chem.* **1992**, *57*, 766.

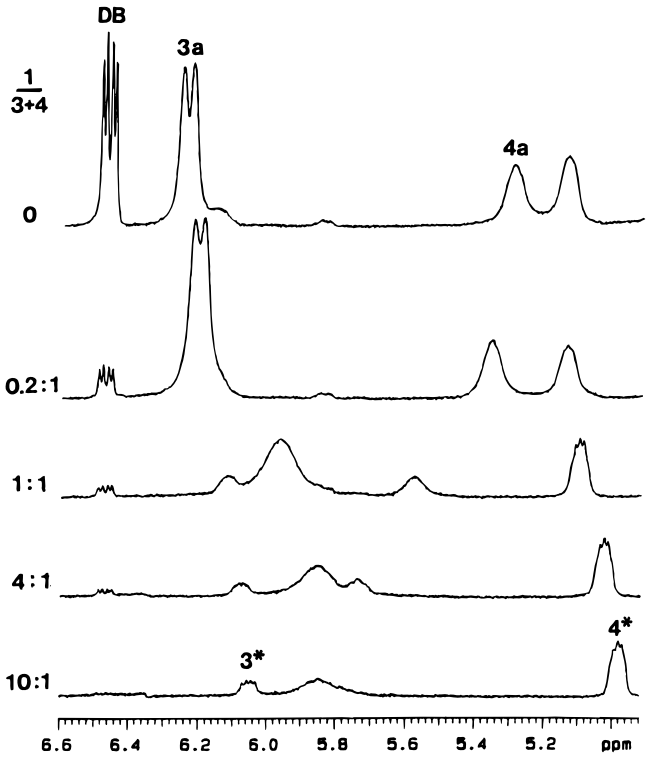


Figure 3. ^{1}H NMR spectra of a mixture of **1**, **3a**, and **4a** for different **1**/(**3a** + **4a**) ratios, ranging from the absence to a 10-fold excess of **1**. Only the PhC*H*O region is shown. **DB**: 1-phenyl-1,2-ethanediol bis(*p*-nitrobenzoate).

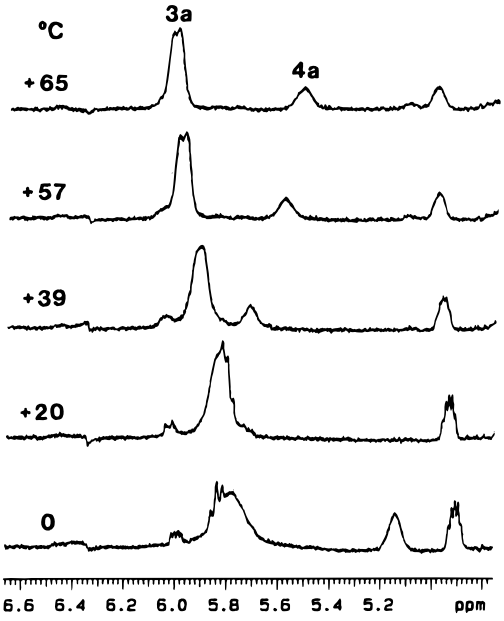
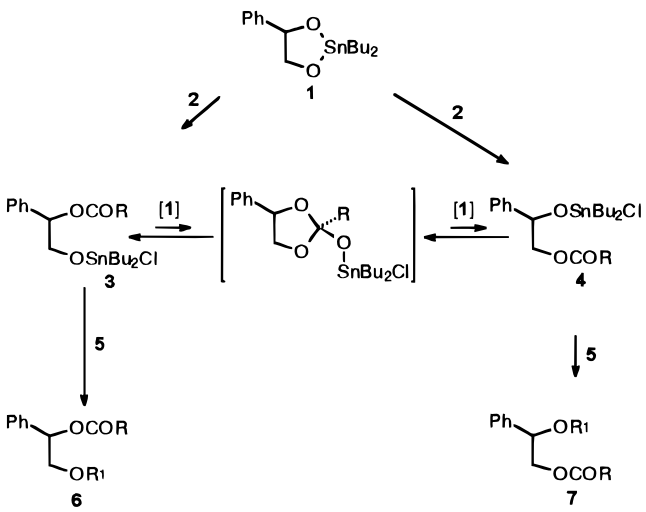


Figure 4. ^{1}H NMR spectra of a mixture of **3a** and **4a** at various temperatures in the presence of a 10-fold excess of **1**. Only the PhC*H*O region is shown.

freezing occurred below rt. The described results lead to the formulation of a mechanism in which, after the initial esterification step, complexation between **1** and the stannyl monoesters **3** and **4** generates the active species responsible for transesterification catalysis (Scheme 6). Apparent inconsistencies thus find an explanation, since increasing concentration of **1** increases the amount of active species, with corresponding rate increase; on the other hand, temperature increase favors dissociation of complexes, thus slowing the exchange rate. In this context, broadening of lines observed in the spectra of

Scheme 6



stannyl esters should be ascribed to the fast equilibria of formation of the complex between **3** (and **4**) and **1**, rather than to the transesterification equilibrium itself. In the subsequent quench step, **3** and **4** are captured into the corresponding stable regioisomers, according to their specific reactivity toward **5**. The secondary monoester **3** is therefore expected to react faster than **4**, because of the higher reactivity of the primary oxygen when compared to the secondary. For comparable rates of intramolecular transesterification and quench, the final product distribution is determined by a combination of relative rate and equilibrium constants, configuring a Curtin−Hammett-type reaction scheme,[15] in which the more the secondary monoester **6** accumulates, the larger the amount of **3** at equilibrium *and* the faster this is established as compared to quench. The actual selectivity toward the secondary monoester **6** will range from a minimum, corresponding to the equilibrium position determined by the temperature, to a maximum of 100%, depending on whether quench will be very much faster or slower than equilibration, respectively. It appears that the elucidation of the reaction mechanism allows for a rationalization of the reversal of chemoselectivity and a correct tuning of conditions to achieve optimum selectivity.

According to the pathway described in Scheme 6, the first esterification step should preferentially afford the primary monoester **4**, owing to the greater reactivity of primary *vs* secondary oxygens; **4** would subsequently isomerize to the secondary monoester **3** through the 5-membered tetrahedral intermediate.[16] If this were true, it should, in principle, be possible to observe the initial formation of **4** and its subsequent isomerization to **3**. Thus, **1** was reacted with 1 equiv of **2a** at −40 °C, monitoring the formation of **3a** and **4a** *vs* time. The results reported in Figure 5 show the initial preferential formation of the primary monoester **4a**, which evolves into the secondary **3a** and approaches the equilibrium position in ca. 1 h. At this stage, variable temperature

(15) For a comprehensive review on the Curtin−Hammett principle and its analytical description, see: Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

(16) Although tetrahedral intermediates have been established for intramolecular reactions of substituted ethylene glycols (see, for example: (a) Santry, L. J.; Azer, S.; McClelland, R. A. *J. Am. Chem. Soc.* **1988**, *110*, 2909. (b) McClelland, R. A.; Seaman, N. E.; Cramm, D. *J. Am. Chem. Soc.* **1984**, *106*, 4511), the present data do not allow the assessment of this species as a real intermediate or a transition state.

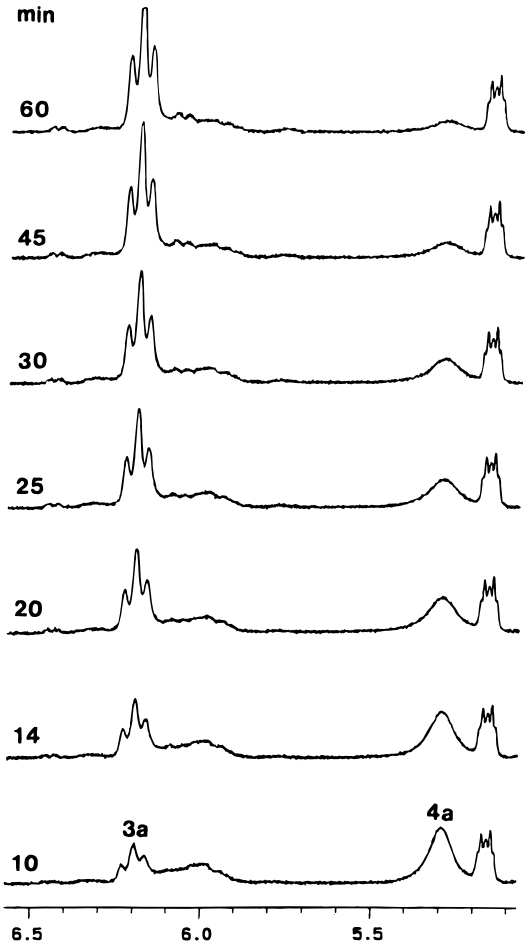


Figure 5. Reaction of **1** with **2a** at −40 °C monitored by ^{1}H NMR *vs* time. Only the PhC*H*O region is shown.

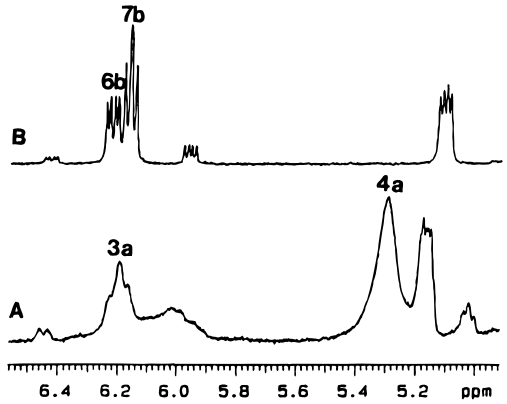
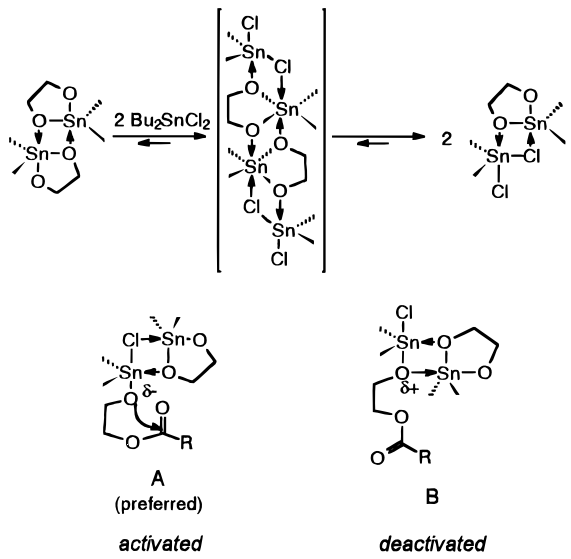


Figure 6. ^{1}H NMR spectra of (A) reaction mixture of **1** with **2a** after 10 min at −40 °C and (B) reaction mixture of A quenched at −40 °C with **5b** (spectrum at rt). Only the PhC*H*O region is shown.

experiments on the sample up to 52 °C showed the expected reversible shift of the equilibrium position, along with the slow formation of diester at the highest temperatures. In a parallel experiment, the acylation mixture, prepared and quenched with acetyl chloride both at −40 °C, gave diesters **6b** and **7b** in a 0.65:1 ratio (Figure 6). Thus, formation of the primary monoester at low temperature and quench of the mixture before equilibration can take place affords products preferentially acylated on the "natural" primary oxygen, providing an unambiguous check for the proposed mechanism.

Scheme 7



The Catalytic System. Convincing evidence of the formation of a complex between the starting dioxastannolane and the stannyl esters and of its ability to catalyze isomerization has been presented. Although the structure of such a complex is not yet experimentally available, a model that accommodates the present data can be inferred.

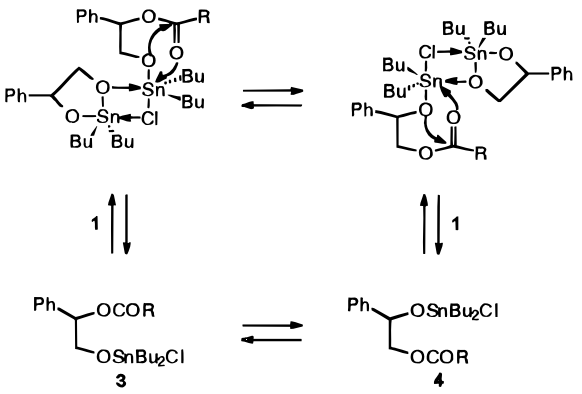
Dioxastannolanes have been shown to form aggregates in solution by associating on Sn−O bonds; aggregates, predominantly dimers, self-stabilize by expanding coordination at tin up to five and six.[17] In the presence of Bu_2SnCl_2, deaggregation occurs to form a 1:1 adduct between the latter and dioxastannolane,[8,11] indicating that binding of chloride to tin stabilizes the stannyl species to a greater extent than binding of oxygen (Scheme 7). Analysis of spectra of dioxastannolane **1** in the presence of Bu_2SnCl_2 analogously showed deaggregation and formation of a 1:1 complex with the latter. Shift of signals, reaching a maximum for a 1:1 molar ratio, was markedly larger for CH_2 than for C*H*, indicating that the complex is preferentially formed on the less hindered Sn−O bond. While dioxastannolanes themselves are unable to exert catalytic activity,[18] adducts between dioxastannolanes and dibutyltin dichloride have been shown to efficiently promote transesterification reactions.[8,11,18]

Using this information to model the active species responsible for the intramolecular interconversion of the stannyl intermediates **3** and **4**, it appears that of the two possible binding modes, depicted as A and B in Scheme 7, the former is preferred, involving one stabilizing Sn−Cl interaction. This binding mode should activate the reagent toward intramolecular nucleophilic addition to the carbonyl, by enhancing the negative charge density on the stannylated oxygen; the reverse should occur to the disfavored adduct, which should be deactivated by the electron-withdrawing effect of tin on the nucleophilic oxygen. This model is in agreement with the reactivity observed in transesterification, which follows the electronegativity order of ligands on the five-coordinate tin. Thus, the stabilization provided by the binding of ligands on tin is the driving force to the formation of the activated

(17) (a) Roelens, S.; Taddei, M. *J. Chem. Soc., Perkin Trans 2* **1985**, 799. (b) Luchinat, C.; Roelens, S. . *J. Am. Chem. Soc.* **1986**, *108*, 4873. (c) Luchinat, C.; Roelens, S. *J. Org. Chem.* **1987**, *52*, 4444.

(18) Roelens, S. *J. Chem. Soc., Chem. Commun.* **1990**, 58.

Scheme 8



stannyl ester A, while the reactivity of the latter decreases with decreasing electronegativity of ligands. Scheme 6 can thus be expanded to include the equilibria reported in Scheme 8.

This model also accounts for the relevance of steric effects in this reaction. It can be seen in fact that the bulk of the stannyl group increases dramatically in the adduct. Such a conspicuous steric hindrance is reasonably the cause that biases the equilibrium toward the secondary monoester in order to relieve strain. Having the concentration ratios of the two regioisomers available with reasonable accuracy in a significantly large temperature range, an estimate of the stability gap between the interconverting monoesters **3a** and **4a** can be attempted. A plot of the ln K values *vs* $1/T$ for the equilibrium constants measured from NMR data in the investigated range of temperature gives van't Hoff plot of good linearity ($r = 0.981$), with $\Delta H° = 4.2$ kcal mol^{-1} and $\Delta S° = 12.8$ eu. The enthalpy difference provides a quantitative estimate of the preference for the most stable secondary monoester, while the unexpectedly large entropy difference that favors the primary monoester accounts for the efficient compensation of contributions, which level off at ca. 50 °C to afford equally abundant regioisomers.[19]

In conclusion, the structure proposed for the catalytic adduct is consistent with the observed reactivity, explains steric effects, and adequately represents the key intermediate responsible for the reversal of chemoselectivity.

Conclusions. The investigation of the mechanism of the organotin-mediated monoacylation of diols has revealed that product distribution is determined by an interplay between kinetic and thermodynamic control over a three-step pathway in which the dibutylstannylene acetal of the starting diol plays the double role of reagent and catalyst. The initially formed primary stannyl monoester isomerizes to the secondary regioisomer, thermodynamically more stable regioisomer, by over 4 kcal mol^{-1}, through a fast intramolecular transesterification equilibrium. Subsequent treatment with a quenching reagent affords increasing amounts of a secondary monoester the slower the quench. It has been shown that selectivity can be optimized up to complete formation of the secondary monoester by appropriately tuning the reactivity difference between the acylating and the quenching reagents. Thus, reversal of chemoselectivity has been explained on the basis of the Curtin−Hammett principle. It has been ascertained that the stannylation procedure highly chemoselectively activates hydroxyl groups toward acyl reagents, particularly acyl halides. The reactivity of the Sn−O bond has been found to follow the electronegativity order of ligands on tin, while halide ligands have been found essential for reversal of chemoselectivity. A structure has been proposed for the catalytic species that accounts for steric effects and the observed reactivity.

Experimental Section

Materials. 4-Phenyl-2,2-dibutyl-1,3,2-dioxastannolane (**1**) was prepared and purified as previously described.[17b] Acetyl chloride (Carlo Erba RPE, 99+%), benzoyl bromide (Aldrich, 97%), bromoacetyl chloride (Aldrich, 98%), 4-nitrophenyl acetate (Fluka, >99%), *p*-anisoyl chloride (Aldrich, 99%), and methyl trifluoromethanesulfonate (Aldrich, 99+%) were used without further purification. 4-Nitrobenzoyl chloride (Aldrich, 98%) was used as such or purified by filtering off the insoluble fraction of a concentrated solution in toluene and subsequently evaporating the solvent. Chlorotrimethylsilane (Carlo Erba RPE) was used as such or distilled over quinoline. Methanesulfonyl chloride (Aldrich, 99+%) was purified by distillation.

General. Standard acylation and quench procedures, isolation, and characterization of products have been described elsewhere.[6] All reactions were run in $CDCl_3$ (Merck, 99.8%) stored on activated 13 X molecular sieves and Ag foil. Room temperature ^{1}H NMR spectra were run at 200 MHz. Variable temperature experiments and kinetic measurements were carried out at 300 MHz. Reactions were performed in 5 mm screw-capped NMR tubes, mixing the reactants with syringes through a septum cap. Variable temperature experiments were carried out under an inert atmosphere; this was not necessary for room temperature experiments. For all the experiments, mixing of reactants was carried out batchwise by injecting the solution of one reagent onto the other, neat or in solution depending on the reactivity of the substrate, so as to achieve a 0.3 ± 0.1 M concentration in each of the two reagents. Subsequent quench was carried out quantitatively by transferring with a syringe the mixture into a second screw-capped tube containing the appropriate amount of quenching reagent. Reproducibility of the results was checked by performing each experiment at least in duplicate and using different lots of reagents when possible. Taking into account variable extent of adventitious hydrolysis and diester formation due to reactants unbalance, results were satisfactorily reproducible.

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(19) It must be emphasized, however, that the reaction scheme consists of a system of multiple equilibria that, besides intramolecular transesterification, involve association processes with **1**. According to this scheme, the measured concentration ratios are not directly amenable to a "true" equilibrium constant, but only to an "apparent" global constant. Thus, thermodynamic parameters may appear anomalous in value, being the net result of a complex situation. The entropy difference, in particular, exhibits an unexpectedly large value for an isomerization reaction; this might be due to contributions from dissociation equilibria, reasonably unbalanced between the two isomers. Clearly, the multiple equilibria system is too complex for a quantitative treatment. Analytical relationships show however that concentration ratios are dependent, *inter alia*, on the equilibrium concentration of **1**; the estimated thermodynamic parameters are therefore meaningful for the set of conditions used, but may vary with the concentration of **1**. Fortunately, such does not seem to be the case, as shown by the experiment described in Figure 3, so that the overall thermodynamic analysis is correct.