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# UNPRECEDENTED OBSERVATION OF LACTONE HYDROLYSIS BY THE $A_{Al}2$ MECHANISM

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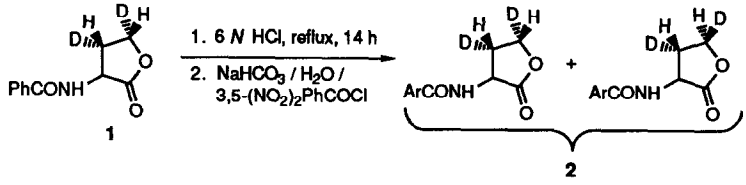
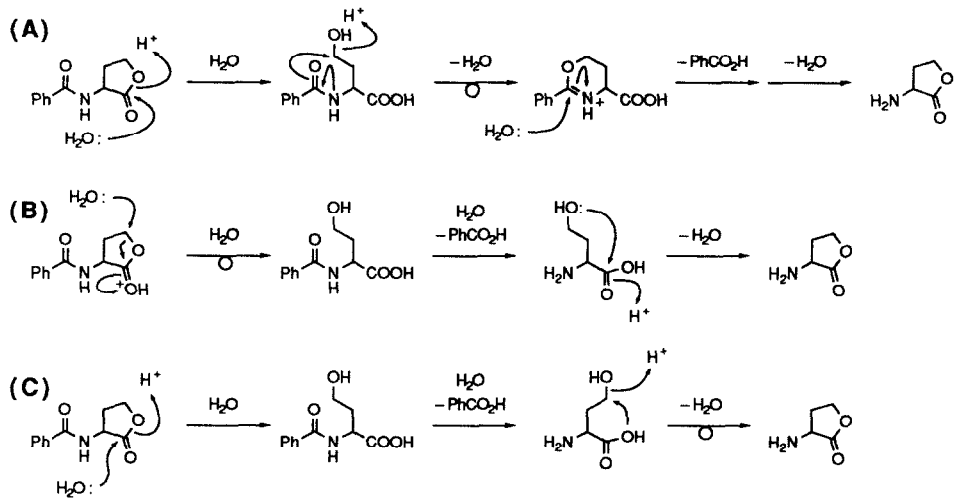
***Abstract:*** *Five-membered lactones are shown to undergo exchange of the ring oxygen when heated at reflux in 6 N HCl / $H_2{}^{18}O$. It is concluded that lactones can be hydrolyzed by the previously unreported $A_{Al}2$ mechanism.*

We have reported that (2*RS*,3*S*,4*S*)-*N*-benzoyl-[3,4-$^2H_2$]homoserine lactone (**1**) undergoes partial epimerization at C-4 (but *not* C-3) during the course of its conversion to *N*-(3,5-dinitrobenzoyl)homoserine lactone (**2**) (Scheme 1).[1] This phenomenon is attributed to the acid-catalyzed hydrolysis of *N*-benzoylhomoserine lactone, since it does not occur when a saponification-acidification sequence is substituted in the reaction sequence for the step in question.[1] We now present evidence that the partial epimerization stems from lactone hydrolysis via (in part) the heretofore undetected $A_{Al}2$ mechanism.[2,3]



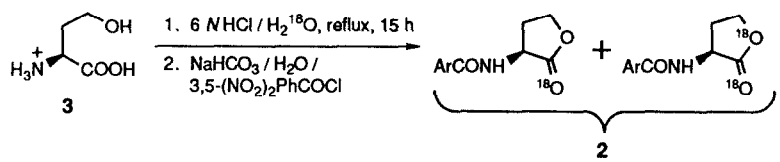

**Scheme 1**

That epimerization is only partial implicates competing mechanisms of lactone hydrolysis, with (presumably) the usual $A_{Ac}2$ mechanism predominating. The $A_{Ac}2$ mechanism for acid catalyzed lactone hydrolysis predicts retention of configuration at C-4, since no bonds to C-4 are broken or made. To rationalize our prior observation, three alternative mechanisms were considered (Scheme 2).[1] These are (A) neighboring group participation; (B) $A_{Al}2$ lactone hydrolysis; and (C) a mechanism involving "normal" $A_{Ac}2$ lactone hydrolysis followed by aberrant reclosure (the reverse of the $A_{Al}2$ mechanism for hydrolysis). Of these, mechanism (A) was considered the most likely, since it is well precedented in other systems.[4,5] To test it, *N*-[*benzoyl*-$^{18}$O]**1** was hydrolyzed under the same conditions that had resulted in epimerization of [3,4-$^2H_2$]**1**. Since no $^{18}$O was incorporated into the product, mechanism A had to be rejected.[1]



**Scheme 2**

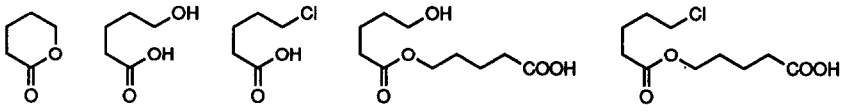
To evaluate the $A_{Al}2$ mechanism, L-homoserine (**3**) was heated at reflux in 6 *N* HCl/$H_2{}^{18}O$, and the resulting lactone was derivatized with 3,5-dinitrobenzoyl chloride, yielding [$^{18}O$]**2** (Scheme 3). (Aside from the labeled reaction medium, these are the same conditions that had resulted in epimerization at C-4 of [3,4-$^2H_2$]**1**.[1]) When **2** was analyzed *via* $^{13}C$ NMR spectroscopy, *both* the lactone ring C-1 and C-4 resonances were found to exhibit $^{18}O$-induced upfield shifts.[6-8] The observed isotope-induced shifts of 0.026 ppm for C-4 and 0.013 ppm and 0.026 ppm for C-1 (indicating attachment of C-1 to one and two $^{18}O$ atoms, respectively) are comparable to those reported in the literature for simple esters.[7,9] (Those carbons without bonds to oxygen exhibited identical resonances in the spectra of labeled and unlabeled **2**.) The mass spectrum (CI/isobutane) of $^{18}O$-labeled **2** was consistent with the NMR data. Two protonated molecular ion peaks, at *m/z* 298 and 300, corresponding to [$^{18}O_1$]**2** and [$^{18}O_2$]**2**, respectively, were observed.



**Scheme 3**

To probe the generality of the $A_{Al}2$ mechanism for lactone hydrolysis, the acid catalyzed hydrolyses of 4-hydroxy-2,2-diphenylbutanoic acid γ-lactone (**4**) and 5-hydroxypentanoic acid δ-lactone (**5**) were studied. Lactone **4** was chosen because the bulky substituents at C-2 ought to maximize ring opening by the $A_{Al}2$ mechanism at the expense of the $A_{Ac}2$ mechanism. Owing to the limited solubility of **4** in aqueous HCl, the reaction was conducted in a 1:1 mixture of 6 *N* HCl/$H_2{}^{18}O$ and *p*-dioxane. Mass spectral analysis of samples taken from the hydrolysis mixture at 1, 2, 4, and 7 days revealed the rapid incorporation of a single atom of $^{18}O$, and a slower rate of formation of [$^{18}O_2$]**4**. The pseudo-first-order rate constant for the formation of [$^{18}O_2$]**4** from [$^{18}O_1$]**4** under these conditions was 0.0025 $h^{-1}$. The fact that exchange of $^{18}O$ into **4** was considerably slower than exchange of $^{18}O$ into **3** presumably owes to the presence of the organic cosolvent.[10]

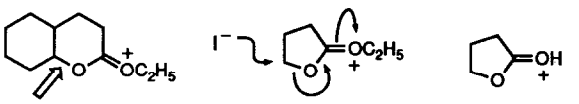
Hydrolysis of 5-hydroxypentanoic acid δ-lactone (**5**) led to a complex mixture of products. The CI/isobutane mass spectrum of the crude product obtained from heating **5** at reflux with unlabeled 6 *N* HCl for 24 hours exhibited several peaks at *m/z* ratios higher than that of the protonated molecular ion corresponding to **5** (which was the base peak). These peaks had the correct *m/z* values for open-chain hydroxyacid **6** and chloroacid 7. Minor peaks, assigned to esters **8** and **9** were also observed. While the products were not characterized any further, the fact that a mixture was obtained indicates that the reaction is considerably more complex than were the hydrolyses of γ-lactones **1** and **4**.



**5** **6** **7** **8** **9**

An alternative explanation of the lactone epimerization and exchange that we have observed is that the protonated ω-hydroxyl group of the hydroxyacid (in equilibrium with the lactone) undergoes $S_N2$ attack by water. This hypothesis can be rejected, however, since 3-amino-1-propanol (a model for homoserine) that had been heated at reflux in 6 *N* $HCl/H_2{}^{18}O$ for 16 hours gave an *N*-(3,5-dinitrobenzoyl) derivative that bore essentially no $^{18}O$.

Treatment of **3** with refluxing 6 *N* $HCl/H_2{}^{18}O$ is expected to result in the freely reversible lactonization. By the $A_{Ac}2$ lactone hydrolysis mechanism, the recovered lactone should bear only a single atom of $^{18}O$, at the carbonyl position. The principle of microscopic reversibility predicts that incorporation of $^{18}O$ into the *ring* oxygen cannot occur by this mechanism. However, $^{18}O$ can exchange into the ring of the lactone through the $A_{Al}2$ mechanism, affording a sample that is doubly labeled with $^{18}O$ (since the carboxyl group will exchange freely with the labeled medium[11]). The $A_{Ac}2$ and $A_{Al}2$ lactone hydrolysis mechanisms can therefore be differentiated. The NMR and mass spectral data for **2** clearly demonstrate the incorporation of two $^{18}O$ atoms into a substantial proportion of the sample. Indeed, the amount of [$^{18}O_2$]**2** relative to [$^{18}O_1$]-compound is consistent with the extent of epimerization of the deuterated lactone that was observed originally.[1] It should be noted that $A_{Ac}2$ lactone hydrolysis is a reversible process and can occur an infinite number of times without epimerization at the ω-carbon or incorporation of label from $H_2{}^{18}O$ into the ring. On the other hand, *each* $A_{Al}2$ hydrolysis event will lead to *both* epimerization and label incorporation from the medium, and so our results are entirely consistent with that mechanism. Still, the extended reaction times required for observation of these signs of the $A_{Al}2$ mechanism suggest that lactone hydrolysis by that mechanism is a very rare event.



**10** **11** **12**

The fact that the $A_{Al}2$ mechanism occurs at all can be rationalized in terms of stereoelectronics.[12] X-ray crystal structures of several *O*-ethyl-substituted dioxenium ions (e.g., **10**; made from the lactone by treatment with Meerwein's reagent) have shown that the σ-bond between the alkyl carbon and the lactone ether oxygen (denoted by the arrow in structure **10**) is unusually long.[13] This indicates delocalization of the bonding electron pair into the antibonding orbital of the carbonyl group, which would in turn weaken the σ-bond. Indeed, Beaulieu and Deslongchamps have invoked such an argument in explaining the facile $S_N2$ reactions of iodide with unsymmetrical cyclic dioxenium salts (cf. **11**).[14] The difference between these *O*-ethyl-substituted dioxenium ions and the lactones utilized in our study is the size of the substituent on the exocyclic oxygen atom: an ethyl group (cf. **10** or **11**) versus a proton (cf. **12**). Thus, carbonyl-

protonated lactones should exist in an essentially planar form, with the alkyl carbon–ether oxygen bond antiperiplanar to the polarized carbonyl bond. Delocalization of the bonding electron pair weakens the (C-4)—O bond of a γ-lactone, making it more susceptible to attack by water (i.e., ring-opening by the $A_{Al}2$ mechanism).

While nucleophilic opening of lactones *via* the $S_N2$ mechanism is not unusual,[15-23] lactone hydrolysis by the analogous $A_{Al}2$ mechanism apparently is unprecedented.[2,3] However, from the evidence presented here, it appears that γ-lactones can undergo acid-catalyzed hydrolysis by the $A_{Al}2$ mechanism.[24]

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