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Stereoselective Transformation of Cyclodecene-1,4-dione Systems, Derived from Steroids, to the Corresponding spiro-γ-lactones. A Semiempirical MO Study

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Abstract: The thermal and acid-catalyzed intramolecular rearrangement of the (*Z*)- and (*E*)-cyclodecene-1,4-dione compounds deriving from steroids, **2a**,**b** and **3a**,**b**, respectively, proceeds stereoselectively to give the corresponding configurationally different spiro-γ-lactone derivatives, the (5*R*,9*R*)-isomers **4a**,**b** (from the (*Z*)-cyclodecenediones **2a**,**b**) and the (5*R*,9*S*)-isomers **5a**,**b** (from the (*E*)-cyclodecenediones **3a**,**b**). The semiempirical MNDO-AM1 and PM3 molecular orbital methods were applied to elucidate the possible mechanistic pathway of the observed intramolecular process leading to the spiro-γ-lactone structures.

Keywords: seco-Steroids, Molecular rearrangement, Acid catalysis, AM1, PM3.

Introduction

Recently it was reported [1,2] that the stereoisomeric (*Z*)- and (*E*)-6,9-dioxocyclodec-3-enyl derivatives **2a,b** and **3a,b**, respectively (Scheme 1) (obtained by oxidative fragmentation of the C(5)–C(10) bond in 5-hydroxy-8-oxo-8,14-seco-5α-androstane-3β,17β-diyl diacetate (**1a)** (X=H_2, R=OAc) [3,4],

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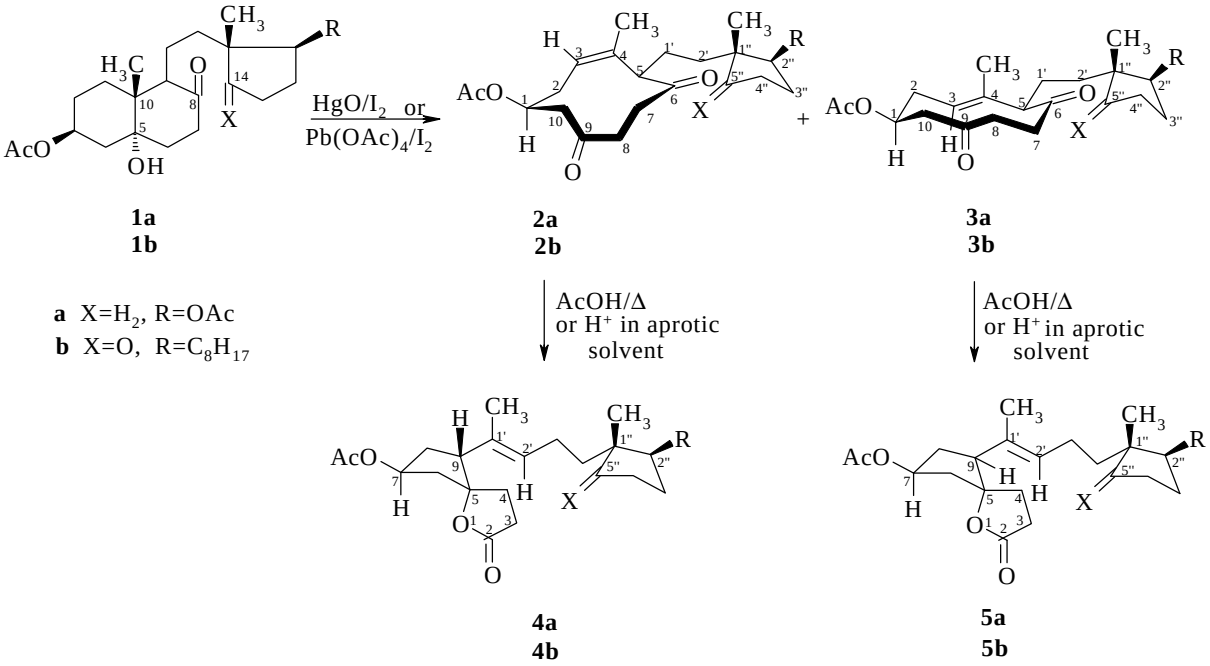
and 5-hydroxy-8,14-dioxo-8,14-seco-5α-cholestane-3β-yl acetate (**1b)** (X=O, R=C_8H_{17}) [5], respectively) upon heating in acetic acid, or under acid-catalyzed conditions, undergo to a new type of intramolecular rearrangement to give the corresponding 1',2'-unsaturated (5*R*,9*R*)- and (5*R*,9*S*)-spiro-γ-lactones **4a,b** and **5a,b**, respectively (Scheme 1 and Table 1).



1a
1b

a X=H_2, R=OAc
b X=O, R=C_8H_{17}

2a
2b

3a
3b

4a
4b

5a
5b

Scheme 1.

Table 1. Products of the thermal and acid-catalyzed reaction of the (*Z*)- and (*E*)-cyclodecenediones **2a**, **3a** and **2b**, **3b**.

Substrate	Conditions Δ/AcOH, r.t. Time (h)	Product[a] yield (%)[b]	Conditions HI/CCl_4, r.t. Time (h)	Product[a] yield (%)[b]	Conditions $HClO_4$/acetone, r.t. Time (h)	Product[a] yield (%)[b]
2a	4	**4a** (66.0)	2	**4a** (77.4)	0.5	**4a** (48.2)
3a	4	**5a** (59.3)	4	**5a** (53.4)	1	**5a** (62.5)
2b	4.5	**4b** (47.6)	1	**4b (**52.4)		
3b	14	**5b** (9.5)	2.5	**5b** (54.3)		

[a] The residue was a complex mixture. [b] The results taken from Ref.[2].

This transformation takes place by participation of three bonds of the respective (*Z*)- and (*E*)-

cyclodecenedione rings, *i.e.*, i) the olefinic C(3)=C(4) bond; ii) the keto carbonyl C(9)=O bond; and iii) the single C(5)–C(6) bond. These bonds are cleaved, while three new bonds are formed, *i.e.*, i) a σ-bond between C(3) and C(9); ii) an ether bond between the C(9) carbonyl O atom and C(6) carbonyl C atom; and iii) a π-bond between C(4) and C(5).

Therefore, the above rearrangement could be formally considered as an "ene-type" reaction. However, the results from Table 1 suggest that, at least when performed in the presence of an acid, it is initiated by protonation, most probably at the C(9) or C(6) oxygen, to give the corresponding oxonium ions of type **A** and **B**, respectively (see Figures 1 and 2). Although for both species an intramolecular rearrangement to the spiro lactones can be envisaged, these processes, depending on the site of protonation, should proceed by two different reaction courses.

In order to elucidate which of these possibilities could be a more reliable pathway to the spiro-γ-lactone structures **4** (from the (*Z*)-isomers) and **5** (from the (*E*)-isomers), the semiempirical MNDO-AM1 molecular-orbital calculations have been carried out.

Method of calculation

As model compounds the stereoisomeric (1*S*,5*R*,*Z*)- and (1*S*,5*R*,*E*)-4,5-dimethyl-6,9-dioxocyclodec-3-en-1-yl acetates (**I** and **V**, Figures 1 and 2), were selected.

The geometries and charge distributions of the molecules were determined by the AM1 method (using a MOPAC package, Version 7.01) [6], employing full geometry optimization and imposing no *a priori* symmetry constraints. The MNDO-AM1 method has proven to be fairly accurate for calculation of molecular properties in various species [6-12]. All transition states were proven by vibrational analysis showing single negative vibration. Simulation of intrinsic reaction coordinates, starting from TS, gives corresponding reactant and product structures. To check the reliability of the structure of the transition states, they were also calculated by a PM3 method.

Results and discussion

(Z)-isomer, I

Reaction intermediates and products of the simulated acid-catalyzed rearrangement of the (*Z*) compound **I** are shown in Figure 1.

Protonation of the C(9) oxygen produces the less stable (with respect to the C(6)=O protonated species **B**-*Z*) intermediate cation **A**-*Z* (–0.205 kcal/mol *versus* –1.449 kcal/mol). In the next step intramolecular C(3)–C(9) cyclization in **A**-*Z*, due to the large separation between the reacting centers, proceeds through an energy rich transition state (TS = 18.049 kcal/mol), to give the C(4) carbo-cationic intermediate **C**-*Z*. The energy partitioning analysis indicates that the weakest bond in **C**-*Z* is its C(5)–H bond, but, deprotonation involving this position would give product **II**. Another possibility, *i.e.*, deprotonation from the 9α-hydroxyl, gives back the starting compound **I**.

In the alternative reaction path the more stable intermediate cation **B**-*Z* (protonated at C(6) oxygen),

is transformed, practically without activation enthalpy to the more stable C(9) carbocationic hemiacetal intermediate **D**-*Z*. In this species the internuclear separation between C(3) and C(9) atoms is 3.069 Å, which is much shorter than the sum of the van der Waal's radii of these atoms (3.7 Å). Therefore, C(3)–C(9) cyclization in **D**-*Z* to the C(4)-centered carbocation **F**-*Z* proceeds with a considerably lower energy (TS = 11.69 kcal/mol) than C(3)-C(9) cyclization in **A**-*Z* (TS = 18.05 kcal/mol). The calculations of transition states were also carried out by a PM3 method, giving almost identical structure, and a very similar vibration pattern [13]. The energy partitioning analysis in **F**-*Z* reveals that C(5)–H is the weakest bond in this species, the deprotonation of which would afford product **III**. However, deprotonation from the 6β-hydroxyl spontaneously leads to the experimentally found spiro-γ-lactone structure of type **IV**.

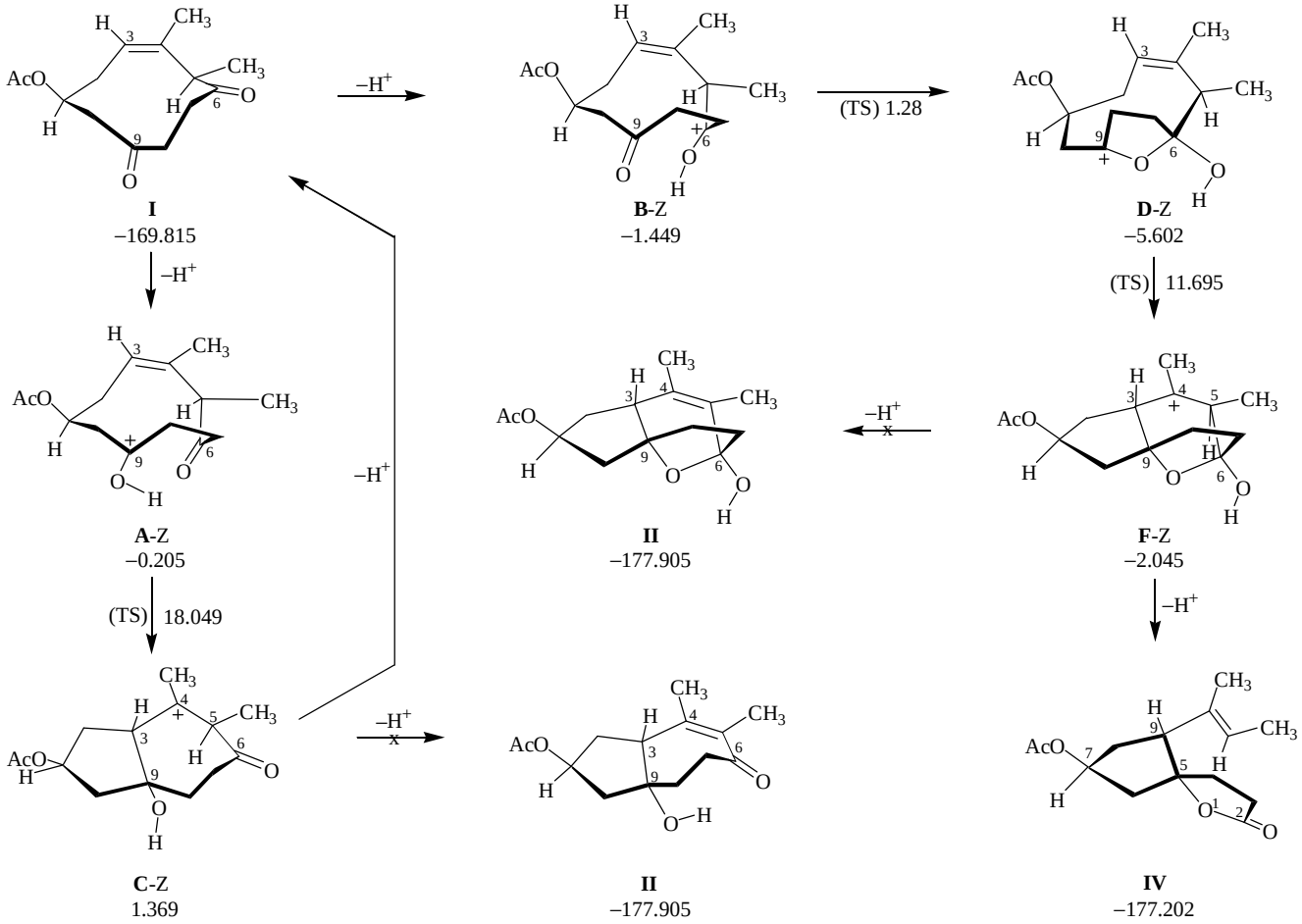


Figure 1. Results of the calculations for (*Z*)-isomer. Heats of formation of the intermediates and products of the corresponding transition states (TS) are given in kcal/mol.

(E)-isomer, V

Reaction intermediates and products of the transformation of the (*E*)-compound identified by AM1 calculations, are shown in Figure 2. The results obtained are analogous to those of the (*Z*)-isomer.

Protonation of oxygen atoms at C(9) and C(6), respectively, yields the corresponding oxonium ions **A**-*E* and **B**-*E*, the latter being more stable than the former (–1.554 kcal/mol *versus* –0.205 kcal/mol). Cyclization of **A**-*E* by formation of the C(3)–C(9) bond affords the cationic intermediate **C**-*E* (TS = 9.639 kcal/mol), which can be stabilized either by elimination of the most labile C(3)–H proton to give compound **VI** or by deprotonation of the 9α-hydroxyl to recover the starting product **V.**

On the other hand, **B**-*E* protonated at C(6) oxygen, is rearranged, *via* the hemi-ketal species **D**-*E*, to the intermediate **F**-*E*. (In order to check the alternative reaction sequences: first formation of C–C, and then of C–O bond, the C(3)–C(9) distance in structure **B**-*E* was treated as the reaction coordinate. With this route the structure **D**-*E* is formed first.) The C(3)–C(9) distance in intermediate **D**-*E* is only 2.514 Å, and consistently, the transition state for conversion to **F**-*E* has low energy (TS = 9.805 kcal/mol). The calculations of transition states were also carried out by the PM3 method, giving almost identical structure, and very similar vibration pattern [14]. In this intermediate, deprotonation involving its weakest (C(3)–H) bond results in formation of the Δ^3-unsaturated compounds **VII**. However, upon deprotonation from the C(6) hydroxyl, the spiro-γ-lactone structure **VIII** is spontaneously formed.

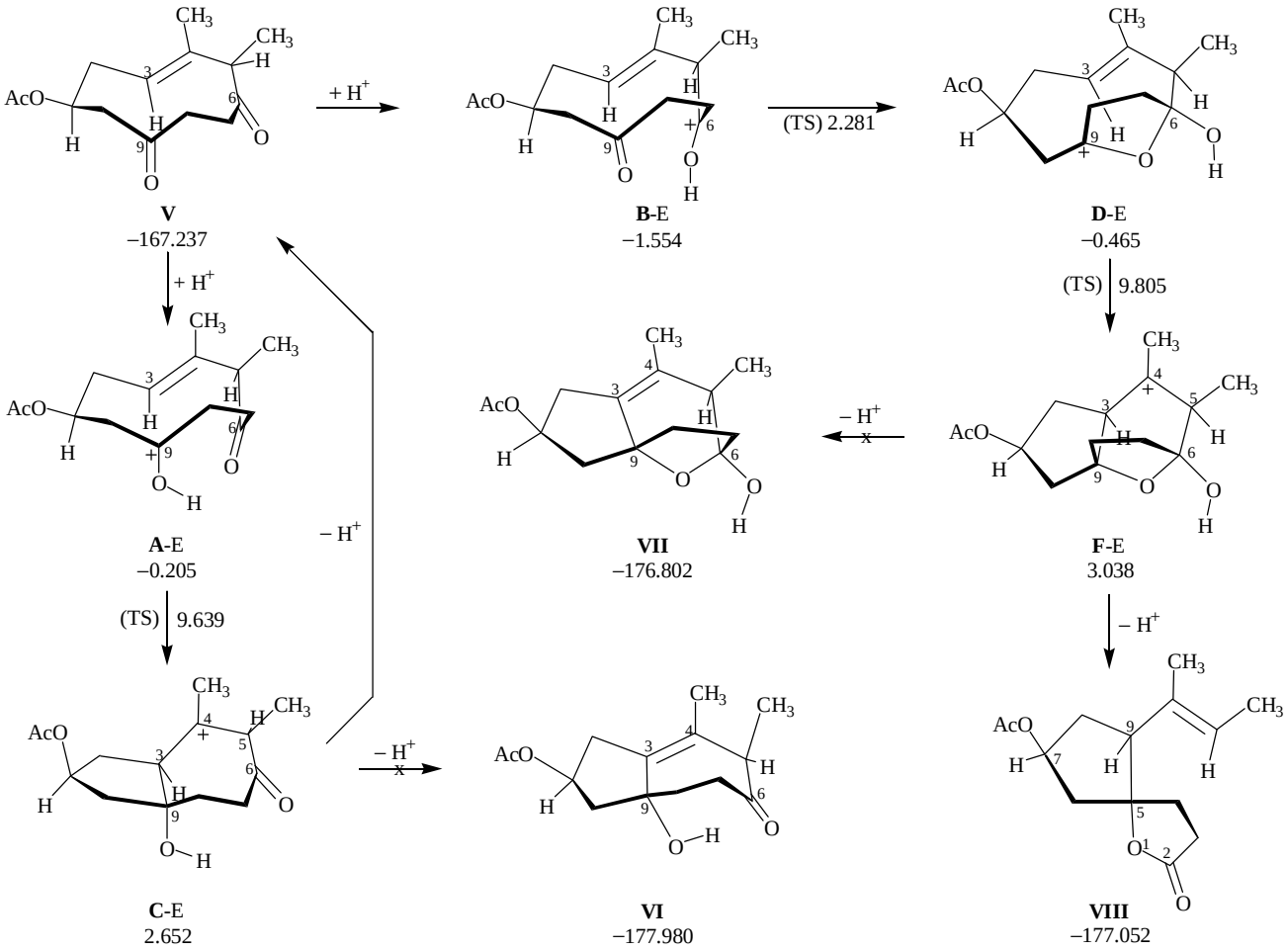


Figure 2. Results of the calculations for (*E*)-isomer. Heats of formation of the intermediates and products of the corresponding transition states (TS) are given in kcal/mol.

The above calculations indicate that intermediates **C** and **F** should be preferentially stabilized by *C*-deprotonation, involving hydrogen in the vicinity of the carbo-cationic site, thus producing compounds **II** and **III** in the (*Z*)-series and compounds **VI** and **VII** in the (*E*)-series. However, the structural analogues of these compounds were not found among reaction products of the steroid (*Z*)- and (*E*)-cyclodecenedione derivatives of type **2** and **3**. As can be seen from Scheme 1, experimentally only products of *O*-deprotonation were identified [15]. This is consistent with the Marcus model of proton transfer, which predicts a much higher rate for proton exchange from the *O*- and *N*-bases, in comparison to the *C*-bases [16-19]. This can be rationalized by a higher positive charge at the hydrogen atom bonded to the more electronegative atom, rather than by the strengths of the respective bonds. In addition, the structures **IV** and **VIII** have more internal rotational degrees of freedom giving rise to a more positive entropy of formation, making their formation thermodynamically preferable.

In both calculated reaction schemes, it is evident that the more convenient reaction path to the spiro-γ-lactone rings **IV** and **VIII**, respectively, involves protonation at the C(6) carbonyl oxygen in the corresponding cyclodecenediones **I** and **V** giving the intermediate cation **B**, followed by isomerization to the intermediate cation **F**. After the removal of hydrogen from the O–H group, a spiro lactone is spontaneously formed. Furthermore, calculations predict that spiro lactones formed from (*Z*)- and (*E*)-substrates should differ in the stereochemistry at the C(9) carbon, exactly as found experimentally.

Experimentally found higher reactivity of (*Z*)-isomers, in the acid catalyzed reaction, exemplified by shorter reaction times (see Table 1), is in accord with the more convenient conformation of the (*Z*)-isomer of intermediate **B** for intramolecular cyclization. The distance between oxygen and carbon atoms that form the ether bond in the next reaction step is shorter in (*Z*)-isomer (2.729 Å) than in (*E*) isomer (2.744 Å). Both distances are considerably smaller than the corresponding van der Waal's distance (3.20 Å).

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15. The *C*-deprotonated compounds of type **II** and **III** in the (*Z*)-series, and of type **VI** and **VII** in the (*E*)-series, if formed at all, could be present as components of the respective complex mixtures (see Table 1), however, in very low yields.
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