Theoretical Study of the Electrocyclic Ring Closure of Hydroxypentadienyl Cations

Olalla Nieto Faza, Carlos Silva López, Rosana Álvarez, and Ángel R. de Lera*[a]

Abstract: At the 6-311G* level of theory, DFT methods predict that the rearrangement of 1,4-dihydroxy-5-methylpentadienyl cation **1** (R = Me) to protonated *trans*-3-hydroxy-2-methylcyclopent-4-en-1-one **2**, an intermediate step in the Piancatelli reaction or rearrangement of furfuryl carbinols to *trans*-2-alkyl(aryl)-3-hydroxycyclopent-4-en-1-one, is a concerted electrocyclic process. Energetic, magnetic, and stereochemical criteria are consistent with a conrotatory electrocyclic ring closure of the most stable *out,out*-**1** isomer to afford *trans*-**2**. Although the *out,in*-**1** isomer is thermodynamically destabilized by 6.84 kcal mol^{-1}, the activation energy for its cyclization is slightly lower (5.29 kcal mol^{-1} versus 5.95 kcal mol^{-1}). The cyclization of the isomers of **1** with the C1-hydroxy group *inwards* showed considerably higher activation energies than their *outwards* counterparts. *in,out*-**1**, although close in energy to *out,out*-**1** (difference of 1.57 kcal mol^{-1}) required about 10 kcal mol^{-1} more to reach the corresponding transition structure. The value measured for the activation energy of *in,in*-**1** (17.32 kcal mol^{-1}) eliminates the alternative conrotatory electrocyclization of this isomer to provide *trans*-**2**. Geometric scrambling by isomerization of the terminal C1–C2 bond of **1** is also unlikely to compete with electrocyclization. The possibility to interpret the **1**→**2** reaction as a nonpericyclic cationic cyclization was also examined through NBO analysis, and the study of bond lengths and atomic charges. It was found that the **1**→**2** concerted rearrangement benefits from charge separation at the cyclization termini, an effect not observed in related concerted electrocyclic processes, such as the classical Nazarov reaction **3**→**4** or the cyclization of the isomeric 2-hydroxypentadienyl cation **5**.

Keywords: density functional calculations · electrocyclic reactions · Nazarov reaction · pentadienyl cation · pericyclic reaction

Introduction

In connection with a project aimed at the development of new modulators for the PPARγ subfamily of nuclear receptors[1] we required access to a series of cyclopentenones bearing some structural similarity to (*S*)-15-deoxy-$\Delta^{[12,14]}$-prostaglandin J_2 (PGJ_2), the most potent natural agonist reported to date.[2] For this synthetic endeavor, we selected the rearrangement of furfurylcarbinols to 2-substituted 3-hydroxycyclopent-4-en-1-ones first described and extensively studied by Piancatelli et al.[3] In all cases examined, treatment of furfurylcarbinols with Brönsted or Lewis acids afforded *trans*-2-substituted-3-hydroxycyclopent-4-en-1-ones, confirming Piancatelli's findings (Scheme 1).[4]

Scheme 1 represents a reasonable mechanistic proposal for this rearrangement, which includes some of the intermediates advanced by Piancatelli et al.[3] Accounting for the stereochemical outcome of the process, a 4π-e$^-$ conrotatory electrocyclic ring closure[5] of a 5-alkyl-1,4-dihydroxypentadienyl cation **1** was postulated. Other intermediates in the sequence, generated by the action of protic (H^+) or Lewis (LA) acids on the starting furfuryl carbinol, are also shown in Scheme 1. Given the fidelity of the transmission of stereochemical information exhibited by pericyclic reactions, the *trans* configuration of **2** requires the conrotatory motion of a pentadienyl cation with both terminal substituents (OH and alkyl) located either *inwards* or *outwards* with respect to the delocalized charged system. The latter structure (**1**) was said to be favored for steric reasons,[3] although no other arguments were provided to support this assumption. At the outset, an alternative conrotatory electrocyclization of isomers of **1** with their terminal substituents oriented either *inwards,outwards* or *outwards,inwards* to afford a *cis*-2-alkyl(aryl)-3-hydroxycyclopent-4-en-1-one, followed by isomeri-

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. Tables with thermodynamic data, NBO charges, and geometries. Some figures mentioned in the text as well as optimized cartesian coordinates for all structures.

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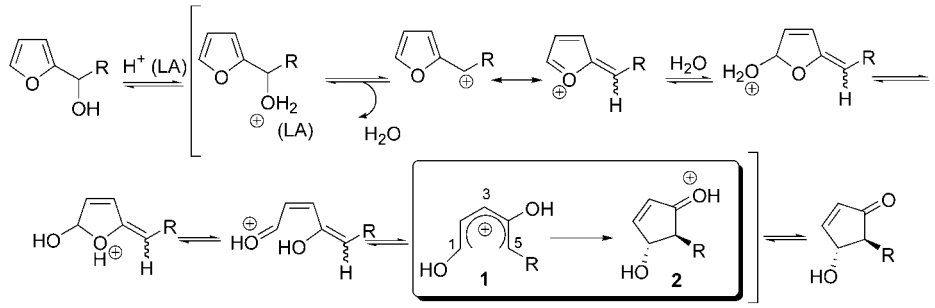


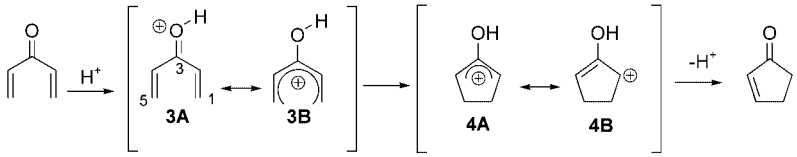
Scheme 1.

zation to the *trans* isomer in the acidic media or during purification could provide the same product of *trans* configuration, complicating the interpretation of the stereochemical outcome.

Being experimentally confronted with the stereochemical features of the Piancatelli rearrangement, we decided to study the reaction as a logical extension of our previous computational work on the electrocyclic ring closure of 1-alkoxyvinyl allenyl cations.[6]

Results and Discussion

We recognized that the mechanism shown in Scheme 1 is reminiscent of the Nazarov reaction[7,8] (Scheme 2) or transformation of divinylketones to cyclopent-2-en-1-ones in

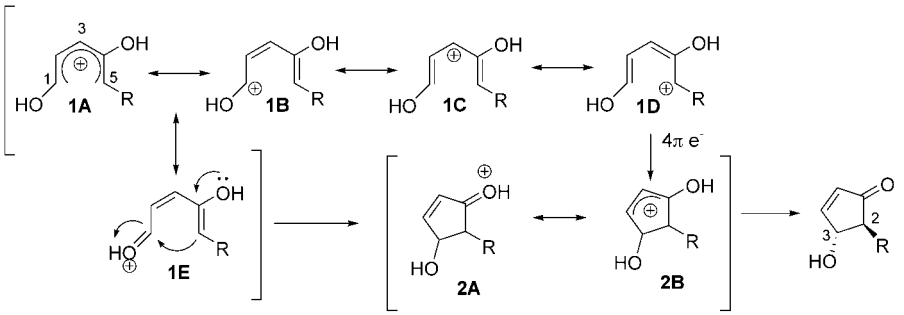


Scheme 2.

acidic media, a reaction that is enjoying renewed interest by the synthetic community.[9,6] In their simplest formulation, both rearrangements (**1**→**2** and **3**→**4**) involve a concerted electrocyclic ring closure of hydroxypentadienyl cations to hydroxycyclopentenyl cations.

The reactions represented in Schemes 1 and 2 differ in the number and location of the hydroxy groups attached to the pentadienyl cation. The Nazarov intermediate **3** has one hydroxy substituent (as oxocarbenium ion) at the central C3 position. Upon cyclization, **3** generates a 2-hydroxycyclopentenyl cation **4**, in which the hydroxy group no longer stabilizes the charge by resonance (it is formally a combination of an enol and a carbenium ion, as shown in resonance structure **4B**). On the other hand, intermediate **1** features a terminal hydroxy group at C1 with oxocarbenium character and an internal hydroxy group at C4,[10] part of an enol function (see resonance structures **1B** to **1E**, Scheme 3). The functionality at C4 in the reactant ends up as an oxocarbenium ion, and that at C1 becomes the secondary alcohol in the protonated hydroxycyclopentenone **2**.[11]

Using resonance-structure-based reasoning, it becomes apparent that the two hydroxy substituents in **1** do not contribute to the same extent to the stabilization of the reactant pentadienyl cation or the product cyclopentenyl cation (Scheme 3). Considering that the reaction coordinate should reflect the different charge-stabilizing effect provided by the heteroatom lone pairs, on addressing the problem from a computational point of view, we first analyzed the influence of the heteroatom by studying the cyclization process for all positional isomers of the hydroxypentadienyl cation parent system. Next, we compared the stabilities of the four stereoisomers of the relevant 1,4-dihydroxy-5-methylpentadienyl cation **1** (R = Me) and determined the geometric and energetic characteristics of their corresponding electrocyclization processes, to understand the structural effects causing the high stereoselectivity of the Piancatelli reaction. Examination of resonance structure **1E** (Scheme 3) suggests a different rationale for the cyclization, namely an intramolecular (acid-catalyzed) aldol reaction of the oxocarbenium ion and the enol functionalities. As reactions of charged species show substantial decrease in activation energies,[12] particularly when they

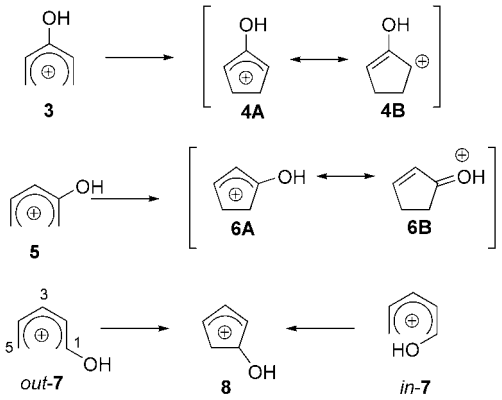


Scheme 3.

benefit from complementary charge separation at the termini of the reacting system, the contribution of charge separation to the description of the reaction paths of these intermediates (**1** and its analogues) was also evaluated. The results of the NBO analysis were confronted with computations on the aromaticity of the transition structures (a characteristic feature of pericyclic processes) as previously

described for related electrocyclizations and heteroelectrocyclizations.[13]

Electrocyclic ring closure of hydroxypentadienyl cations: Although the most stable form of pentadienyl cations is the w-shaped rather than the u-shaped,[14] it is the latter series that are the direct substrates for cyclization, so we selected the s-*cis*,s-*cis* conformer as the starting structure in our study of the rearrangement of hydroxypentadienyl cations **3**, **5**, and **7** to hydroxycyclopentenyl cations **4**, **6**, and **8** (Scheme 4). Two isomers of the 1-hydroxypentadienyl cation, *out*-**7** and *in*-**7** were considered, both leading to the same product **8**.



Scheme 4.

Table 1 lists the corresponding energies, the distance between the cyclization termini in each structure, and the activation energies; data for the same cyclizations investigated in this work previously reported at different levels of theory will be compared where appropriate.[29,15,16] Figure 1 depicts the energy profiles and structures of all relevant species in Scheme 4, as well as the corresponding transition structures.

The structures of reactants **3** and **5** are very similar, with a bond length pattern that depends upon the position of the hydroxy group. Maintaining a common frame of two double bonds between C1–C2 and C4–C5 (as assessed by bond lengths and NBO analysis) there is in **3** a π-interaction between the oxygen and C3 (accounting for its oxocarbenium nature) that is not present in **5**. Although *out*-**7** shows geometric features similar to those of **3** and **5**, such as the C1–C5 distance, or the dihedral angle defined by the C1–C2, and C4–C5 bonds (47, 51, and 56° for **3**, **5**, and *out*-**7**, respectively), it is best grouped with the much more planar structure of the *in*-**7** isomer. Despite the latter having a value of 17° for the same dihedral and a longer C1–C5 distance of 3.50 Å, both structures **7** share a bond pattern that might be best described as composed of a double bond at C4–C5 and a conjugated oxocarbenium ion spanning O-C1-C2-C3.

Table 1. Thermochemical data relative to the lowest energy isomer in each series [kcal mol^{-1}] and distances between C1 and C5 [Å] for the structures depicted in Scheme 4, calculated at the B3LYP/6-311G*// B3LYP/6-311G* level of theory.

Structure	electronic energy	electronic energy + zpve	ΔG	d_{C1-C5}
3	0.00	0.00	0.00	3.19
3ts	21.59	18.69	19.49	2.10
4	−2.86	−2.76	−2.12	1.53
5	0.00	0.00	0.00	3.12
5ts	2.37	−0.06	0.60	2.56
6	−43.62	−41.35	−40.60	1.54
out-**7**	0.00	0.00	0.00	3.16
in-**7**	2.31	2.61	2.11	3.50
out-**7ts**	15.69	12.99	13.93	2.01
in-**7ts**	29.79	26.62	27.44	2.06
7-rotts	27.76	24.14	24.16	3.23
8	6.31	6.26	6.91	1.57

Hydroxycyclopentenyl cations **4**, **6**, and **8** also have similar geometric features, and differences in bond length merely reflect the effect (if any) of the positional permutation of the hydroxy substituent along the cyclopentenyl core on the stability of the allyl cation. The location of the hydroxy group with respect to the charged systems likewise explains the relative stabilities of the cyclization products. The Naza-

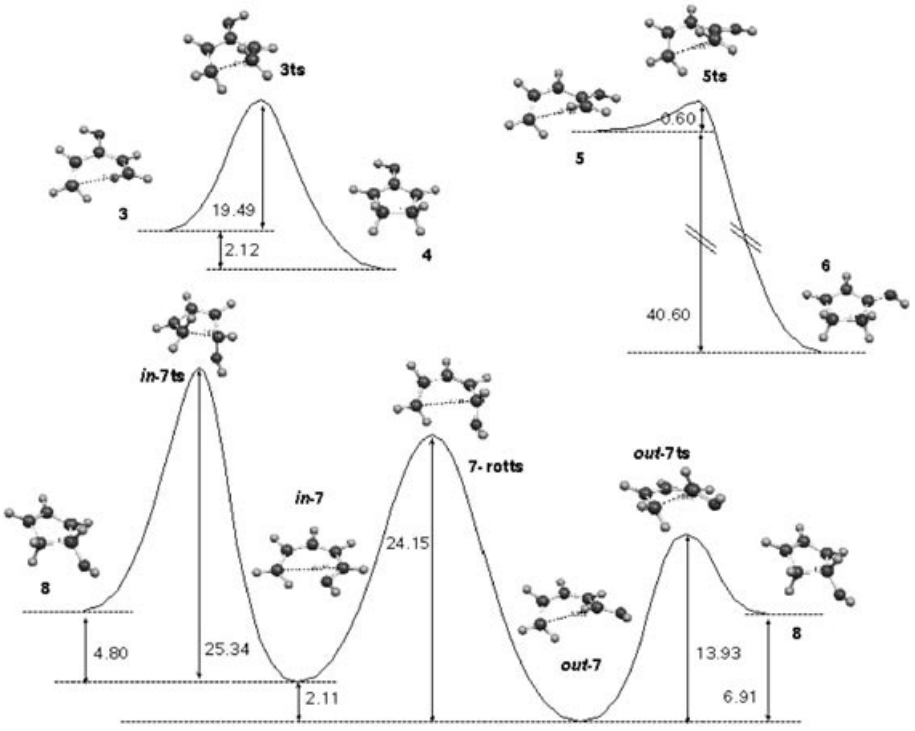


Figure 1. Reaction profiles for the processes depicted in Scheme 4. The reaction energies and activation free energies relative to the most stable structure are given in kcal mol^{-1}.

rov reaction is almost thermoneutral, product **4** being only 2.12 kcal mol^{-1} more stable than the starting cation **3** in its reactive s-*cis*,s-*cis* conformation. The rearrangements of both positional isomers of the 1-hydroxypentadienyl cation **7** are endothermic, and product **8** is destabilized by 4.80 and 6.91 kcal mol^{-1} relative to *in*-**7** and *out*-**7**, respectively. Strikingly, product **6** is 40.60 kcal mol^{-1} lower in energy than reactant **5**.

Analysis of the reaction schemes using resonance theory provides an explanation to the energy differences both between the reactants and between the products. The stabilization provided by the hydroxy substituent is greater when it is placed at the odd positions of the pentadienyl cation, where positive charge concentrates. For the cyclization of substituted pentadienyl cations, there is a displacement of the positive charge from the odd to the even positions along the reaction coordinate, in agreement with previously reported Mulliken population analysis.[15] Donor hydroxy substituents at the even (odd) positions accelerate (retard) the reaction by raising (lowering) the energy of the reactant relative to product-like transition structures. Moreover, donors at C1, as in **7**, retard the reaction since they end up as substituents of tetrahedral carbons, and no charge stabilization by resonance is possible in product **8**. This qualitative estimation predicts the greater stability of the substrate for the Nazarov reaction **3** shortly followed by **7**, while the energy of **5** is the highest. The same reasoning justifies the stability of the cyclopentenyl cations **4**, **6**, and **8**. Resonance stabilization by the heteroatom (oxocarbenium ion) is lost on going from **7** to hydroxycyclopentenyl cation **8**. In contrast, the gain in charge stabilization in **6**, due to the presence of the heteroatom at the terminal position of the allyl cation (a protonated α,β-unsaturated oxocarbenium ion), accounts for its stability. This effect is only moderate for the Nazarov product **4** (Scheme 4).

In all four cases, the conrotatory electrocyclization proceeds through a helix-like transition structure (Figure 1). The computations for the parent Nazarov process **3**→**4** agree well with the results of previous studies[14a,15b,29] in predicting a rather late transition structure, **3ts**, where 66% of the total shortening of the distance between the termini has already taken place. However, whereas the C1−C5 forming bond length in **3ts** and **7ts** is around 2.1 Å, a value found in most pericyclic reactions,[16] that of **5ts** amounts to 2.56 Å, reflecting the early character of this transition state, which originates in part in a rather destabilized reactant.

The activation barriers are fully consistent with the analysis based on differential charge stabilization. Relative to the parent pentadienyl cation, an activation energy penalty of about 15 kcal mol^{-1} has been calculated for the Nazarov reaction, this difference being interpreted as a consequence of the ground-state stabilizing effect provided by the hydroxy group in reactant **3**. A value of 19.49 kcal mol^{-1} was obtained for the conversion of **3** to **4** through **3ts** (cf. 18.89 kcal mol^{-1} at the DFT/6-31G* level[15] and 20.3 kcal mol^{-1} at the MP2/6-31G**//RHF/6-31G* level[29]). For the cyclization of **5**, the hydroxy group at C2 raises the energy of the starting planar cation, leading to a very early transition structure in which the planar geometry of the reactant is only slightly distorted (the C3-C2-C1-H dihedral angle is 167° in **5ts**). This reactant destabilizing effect, together with the complementary stabilization of the resulting cyclopentenyl cation **6** (about 40 kcal mol^{-1} relative to **5**), an extended, highly stabilized oxocarbenium ion, contributes to a reaction profile that is essentially barrier-free (0.6 kcal mol^{-1}).

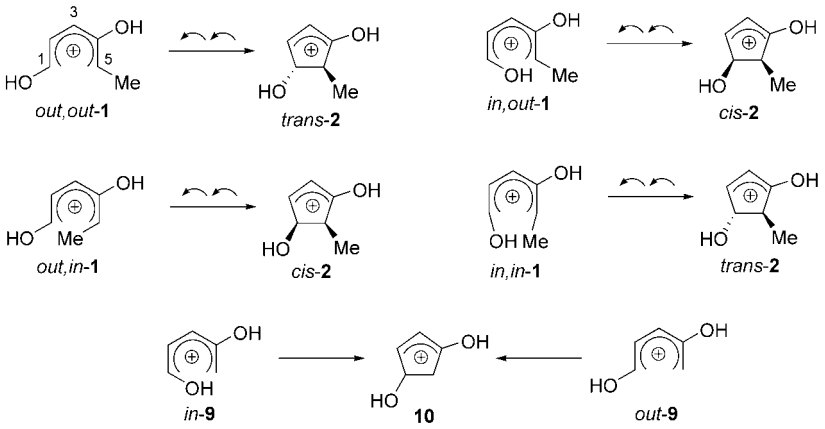
Computations of the reaction profile starting from *out*-**7** reveal a reduction in the activation energy of approximately 5.5 kcal mol^{-1} relative to the Nazarov substrate **3**. On the other hand, the transition structure *in*-**7ts** shows a value of 138° for the C3-C2-C1-H dihedral, which contrasts with the 148–155° calculated for the more regular transition structures **3ts** and *out*-**7ts**; this greater twist places the oxygen atom almost perpendicular to the forming ring. In keeping with previous analysis of electronic effects in electrocyclic reactions by Houk,[17] we attribute the difference in geometries of *in*-**7ts** and *out*-**7ts** to a combination of steric effects and the destabilizing cyclic four-electron interaction between the nonbonding electron pair on oxygen and the forming σ bond in the transition structure of the former. This destabilization is postulated to also contribute to the high activation energy computed for the *in*-**7**→**8** cyclization (25.34 kcal mol^{-1}), which is almost twice as large as that obtained for the cyclization of the *out*-**7** isomer (13.93 kcal mol^{-1}).

For the subsequent analysis of the Piancatelli reaction, the estimation of the barrier for the interconversion of the isomeric cations *out*-**7** and *in*-**7** also becomes relevant. The conformational transition structure **7-rotts** connecting both isomers through a one-bond rotation is located 24.15 kcal mol^{-1} above the most stable *out*-**7**. It can be inferred that isomerization does not compete with the electrocyclic ring closure of *out*-**7**, whereas it is the preferred path for *in*-**7** owing to a difference of 3.30 kcal mol^{-1} between the energy of the transition structures leading to **8** and *out*-**7**.

Solvent effects: Since the experimental reaction conditions for the Nazarov and related processes involve protic or Lewis acids in a polar medium, we considered the simulation of solvent effects to be unavoidable. At this computational level (in the framework of the Onsager method) the effect of polar solvents (acetone, methanol, water) in these reactions proved irrelevant, since stabilization of reactants, transition states (TS), and products seems to benefit from the presence of solvent to the same extent, providing similar geometries and yielding energy differences close to those of the processes in the absence of solvent (see Supporting Information). This can also be attributed to the system being charged. Thus, the high solvation energies of the cations would mask subtler effects that originate from changes in the charge distribution along the reaction path.

The Piancatelli reaction: The results reported for the cyclization of the isomeric hydroxypentadienyl cations **3**, **5**, and **7** provide a sound basis for the discussion of the structural factors operating in the cyclization of the substituted 1,4-dihydroxypentadienyl cation, the relevant intermediate of the Piancatelli reaction. Substrate **1** has structural features common to both model systems **5** and **7**, namely hydroxy

groups at even- and odd-numbered carbon atoms, which are predicted to have opposite effects on charge stabilization along the reaction coordinate. To save computational time, the alkyl or aryl substituents present at C5 in the more complex system depicted in Scheme 1 were replaced by a methyl group. Like the analysis carried out with the C1-hydroxylated substrates **7**, we studied the electrocyclization reactions starting from the isomeric 1,4-dihydroxy-5-methylpentadienyl cations **1** with their terminal substituents oriented either *outwards* or *inwards*. Two descriptors were chosen to distinguish the four isomers of **1**; the first describes the orientation of the C1−OH and the second the position of the C5−Me substituent relative to the pentadienyl system (*cis* and *trans* were not chosen because they can be misleading when treating charged delocalized systems). The conrotatory movements following both symmetry-allowed directions of twist yield enantiomers of the protonated 3-hydroxy-2-methylcyclopent-4-en-1-ones **2**. Although the processes drawn in Scheme 5 only show one enantiomer, both *trans*-**2** and *cis*-**2** diastereomers are racemates.



Scheme 5.

For the sake of completion, and to get a better understanding of the effects of substitution on the five-atom carbon backbone, we also calculated the energy profiles for the rearrangement of 1,4-dihydroxypentadienyl cations **9**, analogues of **1** lacking the terminal methyl substituent.

Table 2 contains the relative electronic energies, electronic energies corrected with the zero-point vibrational energy, thermal energies, and C1−C5 bond lengths for the starting cations **1** and **9**, their cyclization products **2** and **10**, and the transition structures for the electrocyclic reactions and the processes that interconvert the diastereomeric pentadienyl cations of reactants **1** and **9** through one-bond rotation. Figure 2 provides a combined geometric and thermodynamic representation of the available reaction profiles for **1**.

Reactant *out,out*-**1** was found to be the most stable of the geometric isomers, as anticipated through steric considerations, but the *in,out*-**1** isomer with the hydroxy group placed *inwards* is destabilized by only 1.57 kcal mol^{-1} relative to it. The *out,in*-**1** isomer with the bulkier methyl substituent oriented *inwards* is located 6.84 kcal mol^{-1} above *out,out*-**1**. Pointing the hydroxy substituent towards the pentadienyl system is now less costly, since *in,in*-**1** is destabilized by only 0.66 kcal mol^{-1} relative to *out,in*-**1**.

Both isomers of product **2** are more stable than the reactants, and *trans*-**2** is slightly more stable than *cis*-**2** (8.84 and 8.18 kcal mol^{-1}, respectively, relative to reactant *out,out*-**1**).

The transition structures for the allowed conrotatory movements (both directions of twist starting from each isomer **1** are enantiomorphous) are helical, in line with the geometry exhibited by the monohydroxylated systems. The *outwards* or *inwards* orientation of the methyl substituent has only a modest effect in the geometries and energies of the transition structures. *out,in*-**1ts** is reached earlier than *out,out*-**1ts**, with forming bond lengths of 2.45 and 2.29 Å, respectively. The activation energies are roughly similar, 5.29 and 5.95 kcal mol^{-1}, respectively, but are of intermediate value between those required for the cyclization of **5** and *out*-**7**. The opposing interactions of the charged system with C4−OH and C1−OH as the electrocyclization progresses, respectively, results in gain or loss of stabilization, as was previously discussed in model systems **5** and *out*-**7**. The increase in potential energy of *out,in*-**1** relative to isomer *out,out*-**1**, which results from having the larger methyl group

Table 2. Thermochemical data relative to the lowest energy isomer [kcal mol^{-1}] and distances between C1 and C5 [Å] for the structures depicted in Schemes 5 and 7, calculated at the B3LYP/6-311G*//B3LYP/6-311G* level of theory.

Structure	Electronic energy	Electronic energy + zpve	ΔG	d_{C1-C5}
out,out-**1**	0.00	0.00	0.00	3.10
out,out-**1ts**	4.48	4.62	5.95	2.29
trans-**2**	−10.99	−9.77	−8.84	1.56
in,out-**1**	1.98	1.96	1.57	3.47
in,out-**1ts**	16.89	16.39	17.31	2.46
cis-**2**	−10.75	−9.33	−8.18	1.57
out,in-**1**	6.46	6.50	6.84	3.32
out,in-**1ts**	10.41	10.61	12.12	2.45
cis-**2**	−10.75	−9.33	−8.18	1.57
in,in-**1**	6.69	6.78	7.50	3.54
in,in-**1ts**	24.10	23.69	24.83	2.61
trans-**2**	−10.99	−9.77	−8.84	1.56
out,out-**1-rotts**	27.37	26.32	26.39	2.95
in,in-**1-rotts**	30.47	29.60	30.22	3.36
out-**9**	0.00	0.00	0.00	3.11
out-**9ts**	5.45	5.37	6.26	2.38
in-**9**	5.73	5.57	5.32	3.45
in-**9ts**	17.70	17.08	17.72	2.54
9rotts	23.05	22.12	22.40	2.91
10	−15.32	−14.43	−13.99	1.56
out-**15**	0.00	0.00	0.00	2.92
out-**15ts**	7.84	7.73	8.86	1.85
in-**15**	1.40	1.31	1.13	3.00
in-**15ts**	8.71	8.57	9.67	1.96
16	3.41	2.44	3.33	1.54

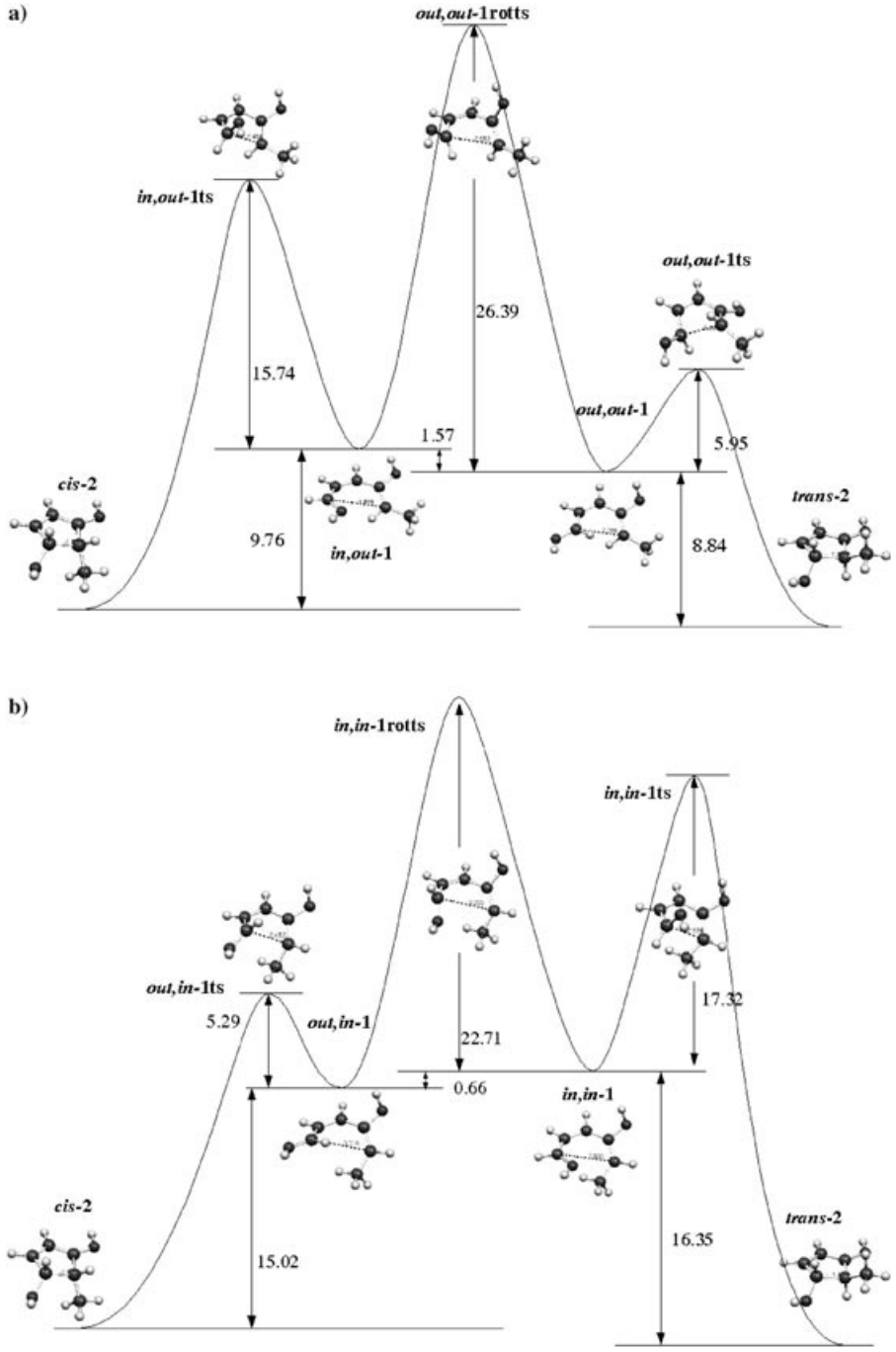


Figure 2. Reaction profiles for the cyclization of the 1,4-dihydroxy-5-methylpentadienyl cation **1**. As the transition structures for the conversion of *in,in*-**1** into *in,out*-**1** and of *out,in*-**1** into *out,out*-**1** could not be located, two graphs (a and b) have been drawn to clarify the different interconversions.

inside, masks the steric congestion at the cyclization termini, resulting in a lower activation energy for this process.

The *inward* terminal OH substituent leads to an even earlier transition structure for conrotation, with bond-forming distances of 2.46 for *in,out*-**1ts** and 2.61 Å for *in,in*-**1ts**. Activation energies are higher than those computed for their OH-*out* isomers (15.74 and 17.32 kcal mol^{-1} for *in,out*-**1ts** and *in,in*-**1ts**, respectively), but again they are lower than the value computed for the cyclization of model *in*-**7** (25.34 kcal mol^{-1}), since they benefit from the effect of the second heteroatom at the even position, as discussed above for **5**. Cyclization of *in,in*-**1**, already destabilized by 7.50 kcal mol^{-1} relative to *out,out*-**1**, showed the greatest activation energy (17.32 kcal mol^{-1}) of the series.

When studying the system without the terminal methyl group, it is found that the barrier for the cyclization of *in*-**9** is considerably lower (12.40 versus 15.74 and 17.32 kcal mol^{-1}, Table 2), while the barrier for the reaction of *out*-**9** is slightly higher (6.26 versus 5.29 and 5.95 kcal mol^{-1}, Table 2) than those measured for the corresponding methyl-substituted analogues. Therefore, it is concluded that the methyl substituent retards the electrocyclization of **1** when the hydroxy group at the opposite terminus is placed *inwards*, but accelerates the process if the reactant has the hydroxy group oriented *outwards*, the magnitude of the retardation being considerably greater (up to 5 kcal mol^{-1}).

In line with the findings for the model systems, the cyclization of dihydroxypentadienyl cations does not benefit from the presence of solvent, since activation energies measured using the Onsager model are roughly similar to the gas phase values in all cases studied.

The similarity in activation energies (0.67 kcal mol^{-1} difference) for the two more accessible cyclization processes starting from *out,out*-**1** and *out,in*-**1**, which differ only by 6.84 kcal mol^{-1} in potential energy, and produce diastereomers of the final product, raises concerns about the stereoselectivity of the Piancatelli reaction. Therefore, the energetics for their interconversion through bond rotation was examined. Despite considerable efforts the transition structures corresponding to bond rotations of the methyl-substituted bond could not be located. Crossing of electronic states in this region cannot be discarded, and we discontinued this reasoning since experimental conditions do not seem to support excited states. However, the transition structures for bond rotation interconverting the geometric isomers by exchange of the terminal hydroxy group and the hydrogen atom at the C1–C2 bond could be located and their energies are consid-

erably higher than those corresponding to the lowest transition state for conrotatory movement: 26.39 kcal mol^{-1} for *out,out*-**1 rotts** (corresponding to the *out,out*-**1** to *in,out*-**1** isomerization), and 22.71 kcal mol^{-1} for *in,in*-**1 rotts** (the isomerization path interconverting *in,in*-**1** and *out,in*-**1**). These transition structures are characterized by the loss of conjugation between the rotating partial double bond and the cationic system, so the diminished conjugation might explain the energy destabilization. It is therefore unlikely that the isomerization manifold competes with the electrocyclic reactions.

Having discarded the interconversion of geometric isomers as a competing reaction, and considering the only moderate solvent effects, the high *trans* stereoselectivity observed for the substrate of the Piancatelli reaction must be traced back to a preferred *out,out*-geometry of the putative cyclizing cation **1**. Mechanisms for acid-induced (i.e. nonthermal) isomerization of the alkyl-substituted terminal double bond are indeed feasible owing to its enol character, and provide a pathway to the *outwards* geometry of the C4–C5 bond. To obtain the *out,out*-geometry of **1**, the opening of the furan ring must be stereoselective to provide the less congested *outwards* orientation of the hydroxy group at the other terminus (C1) of the cyclizing system.

Aromaticity of the transition structures: One of the most intuitive constructs to explain the Woodward–Hoffmann rules for allowance of pericyclic reactions is the aromaticity of transition structures.[18] Based on the high NMR deshielding that characterizes the external positions of aromatic rings, Schleyer et al. proposed a new aromaticity criterion that uses the absolute magnetic shielding (NICS or nucleus independent chemical shift) calculated at the center of the aromatic rings.[19] Cossío et al. reported the evaluation of the NICS at the center of a cyclic saddle point and its variation along the axis perpendicular to the molecular plane to reflect the in-plane aromatic character of transition structures of pericyclic reactions.[13a] They further extended these ideas by showing that the behavior of the NICS along the axis determined by the external magnetic field can be readily rationalized on the basis of the diamagnetic shielding induced by a ring current.[13b] When computed at the same positions, both the NICS and the ring current model provide consistent values. Furthermore, the model has allowed the classification of 6π-e$^-$ disrotatory electrocyclic reactions as having π^1 aromaticity, a picture that indicates the existence of only one ring current circulating at the side of the molecular plane where the disrotatory movement allows a close proximity between the terminal p-AOs.[13c]

For the in-plane aromaticity expected in a conrotatory cyclization like the one represented in transition structures **3ts, 5ts**, and *out*-**7ts**, the ring current model predicts a maximum diamagnetic shielding at the center of the ring. Examination of the NICS values for the Nazarov reaction **3**→**4** and the analogous cyclizations **5**→**6** and *out*-**7**→**8** fully supports this assumption (Figure 3). The best fit between the model[20] and the NICS computations is exhibited by **3ts**, likely owing to the system symmetry. NICS for **5ts** and *out*-**7ts** are slightly lower than for **3ts**, which could be attributed

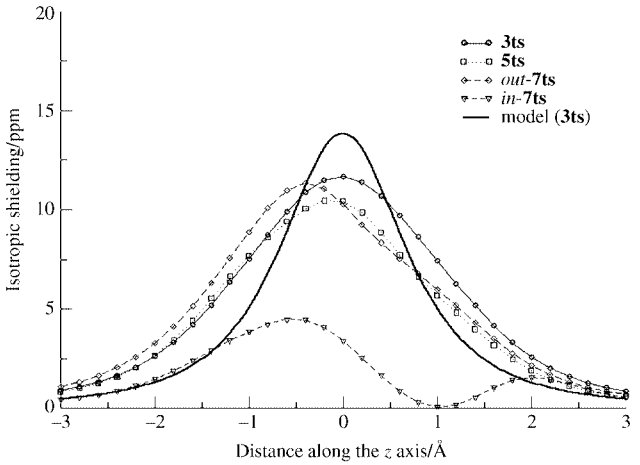
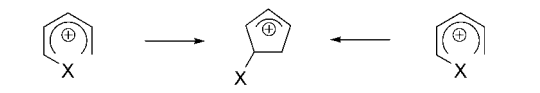


Figure 3. Representation of the NICS versus the distance along an axis normal to the molecular plane that contains the center of the ring, for the cyclization of pentadienyl systems depicted in Scheme 4.

to the charge defect in the rings or to their greater deviation from planarity. The displacement of the maximum NICS value from the molecular plane ($z = 0$) in **5ts** and *out*-**7ts** can be explained by the effect of the ring substituents; these either polarize the charge distribution, distort the transition structure geometry (making the definition of the molecular plane less accurate), interfere with their own charge density when computing points at some distance away from the center, or most likely result in a combination of all these factors.

The deviation of *in*-**7ts** from the rather regular magnetic behavior of the transition structures of its analogues deserves additional comment. In this high-energy transition structure, the NICS values are very small at distances close to the ring center (at 0.5 Å below the ring a value of $\delta = 4.5$ was measured, but the value is $\delta = 0.0$ at 1.0 Å above the ring). We believe that the closed-shell repulsion involving the rotating hydroxy group perpendicular to the incipient ring and the forming σ bond is also reflected in the unique electronic distribution of *in*-**7ts**, in which the aromatic Möbius array of orbitals in the transition state is disrupted by the interaction of the oxygen lone pair.[21]

To better assess the influence that lone pairs on atoms attached to the terminus of a cyclizing system have on the electronic distribution, the isotropic magnetic shieldings were computed for the transition states of the reactions shown in Scheme 6.[22] The data seem to confirm the above reasoning: while the picture does not significantly differ for boranes *in*-**12** and *out*-**12**, because of the absence of the offending electrons, the effect of the nitrogen lone pairs of *in*-**11** on the isotropic magnetic shielding along the selected axis is very strong, leading to a representation that could indicate the existence of antiaromatic interactions (Figure 4).



Scheme 6.

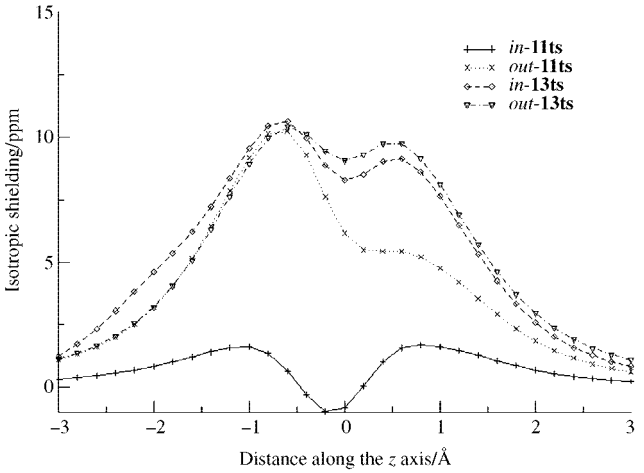
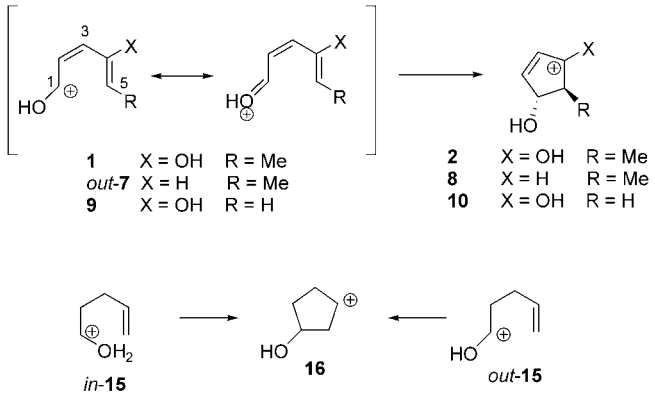


Figure 4. Representation of the NICS versus the distance along an axis normal to the molecular plane that contains the center of the ring for the cyclization of pentadienyl systems depicted in Scheme 6.



Scheme 7.

Table 3. Comparison of the charge difference (in absolute value) between the cyclization termini and the NICS values [ppm], both the maximum ($NICS_{max}$) and that computed at the ring center ($NICS_0$) for the different transition structures.

Structure	|qC1−qC5| (NBO)	$NICS_{max}$	$NICS_0$
3ts	0.01	−11.66	−11.66
5ts	0.13	−10.47	−10.43
out-**7ts**	0.58	−11.35	−10.26
in-**7ts**	0.67	−4.47	−3.40
out,out-**1ts**	0.43	−11.47	−11.47
out,in-**1ts**	0.43	−10.88	−10.88
in,out-**1ts**	0.49	−8.59	−7.70
in,in-**1ts**	0.53	−7.42	−6.83
out-**9ts**	0.66	−9.36	−8.37
in-**9ts**	0.75	−6.20	−4.33

A study on aromaticity, similar to that previously described for model systems **3ts**, **5ts**, and **7ts** was carried out for the transition structures in the Piancatelli rearrangement **1**→**2** (plot available in the Supporting Information, Figure S2). While there is a major variation from the representation in Figure 3, noticeably the very high shielding at distances of about −2 Å, this is only due to the local effects caused by atoms located on or very near the axis where the NICS are evaluated. At shorter distances from the center of the ring the global trends observed are just the same as those of the reactions in Scheme 4: in general, the NICS values are lower than those of the parent Nazarov reaction (Figure 3, **3ts**), the transition states with the C1−OH *outwards* have a certain aromatic character, while the structures with the hydroxy group *inwards* show completely different behavior. The rationale behind this trend has just been discussed.

Pericyclic or ionic reactions? Whereas the Nazarov reaction **3**→**4** and the analogous transformation **5**→**6** can be clearly defined as pericyclic processes, the computational data raise some concerns about the consideration of the cyclizations of the C1-hydroxypentadienyl cations as electrocyclic reactions. For these reactants (**1**, **7**, and **9**) our calculations show a bond pattern (assessed by bond lengths and NBO analysis; see Supporting Information) that can be also represented as an alkene in **7** (or enol in **1** and **9**) and an α,β-unsaturated oxocarbenium ion separated by the C3−C4 single bond (Scheme 7). Since the double bond character of C2−C3 is maintained on going from the reactants to the transition structures, an alternative ionic mechanism could be proposed, in which the oxocarbenium ion is trapped by the π-electrons of the alkene in *out*-**7** (an intramolecular version of the Prins reaction)[23] or by the enol in **1** and **9** (an intramolecular aldol reaction). The considerable charge differences between the carbon atoms that are the termini of the cyclization (Table 3) lend support to the alternative view of the process as an ionic reaction. The charge difference cannot merely be due to the heteroatom, since the same differences calculated between C1 and C3 in **3ts**, or between C1 and C4 in **5ts**, are considerably smaller (Table 3). The charge distribution (assessed by the NBO charges) is consistent with this picture as well, with positive charge concentrated at C1 for the reactants and at C4 for the transition structures and the products. The lowering in activation energies observed along the series **7**→**8** to **1**→**2** (or **9**→**10**) can be readily explained by the stabilizing effect of the hydroxy group in the partially charged C4 position in the transition state of the latter. It could also be argued that the large activation energy differences between the cyclization of the substrates with OH *inwards* relative to those with OH *outwards* (around 10–12 kcal mol^{-1}) are difficult to reconcile using only orbital interaction arguments. Instead, distortion of the saddle point geometries to adopt the trajectories of the ionic process could contribute to the high activation energies for the cyclizations of the *in* isomers.

On the other hand, the NICS values for the transition structures in the cyclization of **1**, **7**, and **9** show a certain degree of aromaticity, and they increase considerably as the reactions progress, becoming twice as large as those computed for the reactants (data not shown). In addition, the normal modes of the imaginary frequencies clearly involve a conrotatory motion of the terminal atoms, and all attempts to locate a disrotatory transition structure were unsuccessful, the search leading to the conrotatory saddle point in all cases. Neither of these two features is exhibited by the cycli-

zation of the saturated analogues **15** to 3-hydroxycyclopentyl cation **16** (Scheme 7), which can be described as the capture of the oxocarbenium ion by an alkene (an intramolecular Prins reaction) even though the transition structures **15ts** are geometrically very similar to **7ts**. Although we would expect a higher activation energy for the cyclizations of **15**, owing to the lack of "orbital stabilization" provided by the aromatic transition states, barriers of 8.86 and 8.55 kcal mol^{-1} were computed for the cyclization of *out*-**15** and *in*-**15**, respectively. The more pronounced charge separation[24] and the better orientation of the oxocarbenium moiety having a tetrahedral center at C2 (the reactants are no longer planar) must contribute to further lowering the activation energy of the Prins processes **15**→**16** relative to the cyclization of the unsaturated fully conjugated systems **7**→**8**. So, even though the energetics of the cyclization reaction involving **15** cannot be easily compared to those of the analogous conjugated systems **7**, the similar energies of activation of both *out* and *in* paths and the absence of termini rotation in *out*-**15ts** and *in*-**15ts** are additional features of ionic processes. In conclusion, these distinctive features, together with the magnetic and stereochemical criteria further reinforce the notion that the **7**→**8** cyclization is a pericyclic reaction. As an extension, and because the transformation of *out,out*-**1** to *trans*-**2** is similar to the cyclization of *out*-**7** to **8** (but more facile owing to the effect of the C4−OH), the Piancatelli rearrangement should equally qualify as a pericyclic reaction.

It has been recently reported that divinyl ketones polarized with a donor group at C2 and an acceptor group at C4 cyclize under mild conditions, in what was considered a modified Nazarov reaction involving a "vinyl nucleophile" and a "vinyl electrophile".[25] In analogy with the design of these Nazarov substrates, intermediate **1** of the Piancatelli rearrangement could also be classified as a polarized pentadienyl cation, with an acceptor group at C1 (oxocarbenium ion) and a donor group at C4 (the enol). The process benefits from charge polarization owing to the presence of a heteroatom at one of the termini carbons, as the NBO bond orders, bond lengths, and atomic charges suggest.

Since, according to the computed activation energies, the rearrangement of intermediate **1** should also take place easily, the rather harsh conditions (for example, heating with polyphosphoric acid in acetone/H_2O at 50 °C for 24 h) used experimentally in the Piancatelli reaction are most likely required for inducing the opening of the furan ring to provide **1**.

Conclusion

Computation of the reaction profile at the B3LYP/6–311G* level of theory for the key step of the Piancatelli reaction, or transformation of furfuryl carbinols to *trans*-2-alkyl(aryl)-3-hydroxycyclopent-4-en-1-ones, predicts its pericyclic nature. Geometric, energetic, and magnetic criteria are compatible with a conrotatory electrocyclic reaction, which transforms intermediate *out,out*-5-alky-1,4-dihydroxypentadienyl cation **1** into protonated *trans*-**2**. Both the Piancatelli and the Nazarov reactions, prototypical 4π-e^- electrocyclizations, primarily benefit from the presence of an array of interacting orbitals in the reactant hydroxypentadienyl cations, as shown by the evaluation of the NICS at distances from the ring plane in the helical transition structures for their conrotatory motions. Charge separation at the terminal carbon atoms in **1** further contributes to reduce the activation energy for its cyclization. Similar studies on a model system lacking the cyclic array of interacting orbitals allows a distinction to be made between pericyclic and ionic reactions leading to ring systems of the same size.

Computational Methods

All computations in this study have been performed using the Gaussian 98 suite of programs.[26] To include electron correlation at a reasonable computational cost, density functional theory (DFT)[27] was used. The Becke three-parameter exchange functional[27b] and the nonlocal correlation functional of Lee, Yang, and Parr[27e] (B3LYP) with the 6-311G* basis set were used to compute the geometries, energies, and normal-mode vibration frequencies of the starting cations, the corresponding transition structures, and the products. The density functional method was chosen in view of the previous successful application of this approach to describe the transition structures of other pericyclic reactions[28] and previous DFT calculations for the Nazarov cyclization and its allene variant.[29,6] The stationary points were characterized by means of harmonic analysis, and for all the transition structures, the vibration related to the imaginary frequency corresponds to the nuclear motion along the reaction coordinate under study. In several significant cases intrinsic reaction coordinate (IRC)[30] calculations were performed to unambiguously connect transition structures with reactants and products. Bond orders and atomic charges were calculated with the natural bond orbital (NBO)[31] method. Nucleus independent chemical shifts (NICS)[32] were calculated by means of the gauge-independent atomic orbitals (GIAO) method.[33] The effect of the solvent (water, methanol, and acetone) was taken into account for some of the systems under study through geometry optimizations and frequency calculations using a SCRF model with a spherical cavity, only keeping the dipole term of the multipolar expansion (Onsager model).[34]

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