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Investigation of Transannular Cycloaddition Reactions involving Furanoxonium Ions using DFT Calculations. Implications for the Origin of Plumarellide and Rameswaralide and related Polycyclic Metabolites isolated from Corals.

B. Lygo,* M. J. Palframan* and G. Pattenden*

DFT calculations probing potential (4+2) and (4+3) cycloaddition pathways leading to the polycyclic ring systems found in the coral secondary metabolites plumarellide, mandapamate and rameswaralide are described. Formation of plumarellide and mandapamate via stepwise intramolecular cycloaddition of a furanoxonium ion onto a 1,3-diene is shown to be viable. The calculations also predict the outcome of related cyclisations involving model systems.

Introduction

Plumarellide 1, rameswaralide 2, and the mandapamates 3 and 4 are novel polycyclic secondary metabolites which are believed to share a common biosynthetic origin. The metabolites 1, 3 and 4 have a central cyclohexene ring in their structures, whilst rameswaralide 2 instead has a cycloheptene ring as a key feature of its structure. The compounds also display subtle variations in stereochemistry at their C7 and C8 centres. Thus, the tertiary OH groups at C8 in 2, 3 and 4 are orientated β, whereas the same OH group in plumarellide 1 has the corresponding α-orientation. Furthermore, the H-centre at C7 in the metabolites 1 and 2 is on the α-face of their structures, but the same H-centre in the mandapamates 3 and 4 is on the opposite β-face of their structures.
Scheme 2. Formation of the polycycles 12, 15 and 17 via acid-catalysed rearrangement of the acetonides 10 and 16.

Scheme 3. Stepwise cyclisation pathways to 12 and 14 from the common furanoxonium ion intermediate 13.

In earlier publications we have speculated that the metabolites 1-4 have their origins in furanobutenolide–based cembranoids, i.e. 5, by way of elaboration to novel enol ether intermediates, e.g. 6, followed by transannular (4+2) or (4+3) type cycloaddition reactions, viz. 6→7 and 8→9 (Scheme 1). Indeed, during investigations of these proposals we showed that when the model furanobutenolide 10, having an α-orientated oxy centre at C8 was treated with TFA in CH₂Cl₂ it underwent hydrolysis to the isomeric furanoxonium ion intermediates 11 and 13 which then underwent transannular cyclisation reactions leading to the polycycles 12 and 15 respectively in a combined overall yield of 60% (Scheme 2). Interestingly, treatment of the diastereoisomeric acetonide 16 having a β-orientated oxy centre at C8 with TFA under the same conditions, gave only the cycloheptene ring-containing polycycle 17 and no corresponding cyclohexene ring-containing compound similar to 15.

Although we have represented the cyclisations leading to 12 and 15 taking place by (4+3) and (4+2) type cyclisations, via the isomeric furanoxonium ion intermediates 11 and 13 respectively, we have also suggested that the same overall conversions could be depicted as stepwise carbonium ion cyclisation processes, with the allylic carbonium ion 18 as the key intermediate (see Scheme 3).

Scheme 4. A proposed pathway from the macrocycle 19 to the plumarellide ring system 21.
Initially B3LYP/6-31G(d) stepwise and concerted cyclisation pathways corresponding to the transformations of solvent correction.

Finally, B3LYP/6-31G(d) was used to search for both stepwise and concerted cyclisation pathways corresponding to the transformations 11→12, 13→14, 16→17. Geometric counterpoise (gCP) and dispersion (D3) corrections were applied to all of the structures generated in this way, as recommended by Grimme. All of the structures were also re-optimised using B3LYP/6-31+G(d,p). This method has been widely utilised for DFT-based geometry optimisation in the study of biosynthetic pathways involving carbocation intermediates, and generally performs well when benchmarked against other methodologies. In each case we were only able to locate low energy intermediates that could be generated, i.e. 22 and 23 from 10, and 24 and 25 from 16 (Scheme 5). In the first step of the cyclisations of these furanoxonium ions, each could cyclise to their corresponding allylic carbocation intermediates 26 and 27. In each case cyclisation could occur with the furanoxonium O-atom orientated either exo- or endo- relative to the diene, leading to the four viable stepwise cyclisation pathways shown in Scheme 5. These cyclisations result in the production of two diastereoisomeric carbocation intermediates, i.e. 26/26’ and 27/27’ respectively.

Table 1. Relative Transition State Energies for the Cyclisation Modes Depicted in Scheme 5 (R=Me, R’=OH, i.e. C8 α-hydroxy series).

<table>
<thead>
<tr>
<th>Method</th>
<th>Relative Energy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E-exo</td>
</tr>
<tr>
<td>B3LYP-gCP-D3/6-31G(d)</td>
<td>5.9</td>
</tr>
<tr>
<td>B3LYP/6-31+G(d,p)</td>
<td>4.8</td>
</tr>
<tr>
<td>BMK/6-311+G(d,p)/B3LYP/6-31+G(d,p)</td>
<td>3.9</td>
</tr>
<tr>
<td>M06-2X/6-31+G(d,p)</td>
<td>4.4</td>
</tr>
</tbody>
</table>

For further details see supplementary data. *Based on Gibbs free energy values.

Table 2. Relative Transition State Energies for the Cyclisation Modes Depicted in Scheme 5 (R=OH, R’=Me, i.e. C8 β-hydroxy series).

<table>
<thead>
<tr>
<th>Method</th>
<th>Relative Energy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E-exo</td>
</tr>
<tr>
<td>B3LYP-gCP-D3/6-31G(d)</td>
<td>0</td>
</tr>
<tr>
<td>B3LYP/6-31+G(d,p)</td>
<td>0</td>
</tr>
<tr>
<td>BMK/6-311+G(d,p)/B3LYP/6-31+G(d,p)</td>
<td>0</td>
</tr>
<tr>
<td>M06-2X/6-31+G(d,p)</td>
<td>0</td>
</tr>
</tbody>
</table>

For further details see supplementary data. *Based on Gibbs free energy values.

Predicted relative energies for the transition states of these cyclisation processes are given in Table 1 (for the C8 α-OH series, i.e. from 10) and Table 2 (for the C8 β-OH series, i.e. from 16). We have used the relative energy of the transition states here rather than comparing activation energies because larger errors in the latter would be expected due to the high number of degrees of freedom in the starting furanoxonium ions. IRC calculations on the transition states led to 'starting...
geometries that were typically 8-14 kcal/mol lower in energy, providing an estimate of the minimum barrier to cyclisation. In addition to the methods described above, we also performed BMK/6-311+G(d,p) single point calculations on B3LYP/6-31+G(d,p) optimised geometries and re-optimised the structures using M06-2X/6-31+G(d,p). BMK/6-311+G(d,p)//B3LYP/6-31+G(d,p) was included as this has previously been shown to give good qualitative agreement with experiment when applied to the intermolecular (4+3) cycloadditions of substituted furanoxonium ions to 1,3-dienes. M06-2X/6-31+G(d,p) was included for comparison as this has been widely used in the study of reaction pathways in recent years and would be expected to superior when accounting for weak π-interactions.

Figure 2. Favoured transition state structures for cyclisations of furanoxonium ion intermediates derived from the acetonides 10 and 16. Atom distances are in Å.

Figure 3. Free energy profile for the cyclisation pathways depicted in Scheme 6.

Scheme 6. Cyclisation pathways leading from the allyl cation intermediate 28. Bond lengths (Å) shown are for the new bonds formed.
Figure 4. Free energy profile for the cyclisation pathways depicted in Scheme 7.

Scheme 7. Cyclisation pathways leading from the allylic carbocation intermediate 34. Bond lengths (Å) shown are for the new bonds formed.

The data presented in Tables 1 and 2 suggest that the stereogenic centre at C8 in the starting isomeric furanoxonium ions 22-25 has a strong influence over the preferred mode of cyclisation. In the C8 α-hydroxy series (R1=Me, R2=OH), cyclisation via 24 (Z-exo) or 25 (E-endo) is predicted to be significantly favoured over the alternative pathways. It is notable that these two favoured cyclisation pathways both result in the formation of the same diastereoisomer 27/27’ of the bicyclic intermediate, and that the newly created stereogenic centres match those that result from the in vitro acid-promoted cyclisation of the furanobutenolide 16. In the C8 β-hydroxy series (R1=OH, R2=Me), cyclisation via the furanoxonium ion 22 (E-exo) is predicted to be favoured over the alternatives. This cyclisation would result in the formation of the diastereoisomeric intermediate 26/26’ which, again, is consistent with the outcome of the acid-catalysed cyclisation of the furanobutenolide 10 in vitro (Scheme 2).

The origin of these stereoselectivities appears to be largely down to the relative size of the methyl (A-value 1.74 kcal/mol) and hydroxy substituents (A-value 0.61 kcal/mol) at C8 in 10 and 16, coupled with the requirement for the bulky furyl-fragment to adopt a pseudo-equatorial orientation with respect to the forming cyclopentane ring in the first step of the cyclisation. The three most favoured modes of cyclisation are
represented in Figure 2, and each has the larger substituent (CH$_3$ and furyl) pseudo-equatorial and the smaller hydroxyl group pseudo-axial. In these structures the forming bonds are 2.14-2.18 Å and the carbon atoms that would complete a (4+2) or (4+3) cycloaddition are 3.29-3.43 Å apart.


All the different methods employed for the aforementioned calculations were in qualitative agreement and all suggested the conformational preference of the connecting chain was the main factor determining the stereochemical outcome of the cyclisation. Based on this we concluded that B3LYP/6-31+G(d,p) should be adequate for all subsequent geometry optimisations. We opted to run single-point calculations on optimised geometries using BMK/6-311+G(d,p) to allow comparison with previously published results.  

We next considered the possible pathways that could be followed from the carbocation intermediates 26 and 27 to the polycyclic structures 12, 15 and 17. The results we obtained for the C8 α-hydroxy series, i.e. 16, are shown in Figure 3 and summarised in Scheme 6. They suggest that the most favourable pathway results in cyclisation to the tetracyclic carbocation 29. From here, rapid loss of a proton regenerates the furan ring and leads to 17, the same polycyclic product obtained from the acid-catalysed cyclisation of the furanobutenolide 16 (Scheme 2). Formation of the cyclohexene ring-containing tetracyclic intermediate 32 from 28 is also predicted to be relatively favourable. However, further cyclisation of 32 to the pentacycle 33 is unfavourable due to the highly strained nature of 33. This suggests that if the oxonium ion 32 was formed it would either hydrolyse leading to by-products that have not been identified, or simply revert back to the allylic carbocation 28.  

For the corresponding C8 β-hydroxy series, i.e. from 10, the most favourable pathways that would lead to the products 12 and 15 are shown in Figure 4 and summarised in Scheme 7. It is evident from Figure 4 that very low barrier pathways are predicted for the formation of both of the oxonium ion intermediates 14 and 35. Furthermore, the cyclisation of 14 leading to the pentacyclic structure 38 is also predicted to be favourable. Loss of a proton from each of the intermediates 35 and 38 would then lead to the same polycycles 12 and 15 that were produced earlier following acid-catalysed rearrangement of the furanobutenolide 10 (Scheme 2).  

We next carried out DFT calculations on the cyclisation modes of the macrocycle-based furanoxonium ion 20 and its corresponding cyclic hemiketal 39 leading to the tetracyclic ring system 21 present in plumarellide 1 (Scheme 8; cf. Scheme 4). Our studies with the acyclic systems 10 and 16 have concluded that their conversions to the polycycles 12/15 and 17 respectively, are more likely to involve stepwise processes via carbonium ion intermediates rather than (4+2) cycloaddition reactions. There is also the possibility however that these same cyclisations, and also the cyclisation of the cyclic hemiketal 39 to 21, could take place by stepwise acid-catalysed cyclisations from the enedione tautomer 41 or from a corresponding enol, e.g. 42 of 39. These new cyclisation possibilities, which are summarised in Scheme 8, were investigated alongside the thermal [4+2] and stepwise carbonium ion cyclisations from 20 and 39 using BMK/6-311+G(d,p)/B3LYP/6-31+G(d,p). The outcomes of these calculations are shown in Figures 5, 6 and 7. As expected, the second step in the stepwise cyclisation of the furanoxonium ion 20 (Figure 5) is predicted to have a higher activation energy than the corresponding acyclic system because it leads to a bridgehead carbonium ion, i.e. 44. The stepwise acid-catalysed pathway 39 $\rightarrow$ 40 $\rightarrow$ 21, shown in Scheme 8 and Figure 6, is predicted to be more favourable than the thermal [4+2] cycloaddition (Figure 7), and the stereochemistry produced in the resulting polycycle is a consequence of the conformation of the macrocycle.  

The enedione structure 41 is relatively more stable than its cyclic hemiketal tautomer 39, which is predicted to be relatively more stable than its enol tautomer 42, i.e. relative energies (kcal/mol) 0 : 7.0 : 9.7.

In contemporaneous studies we synthesised the Z-isomer 45 corresponding to 20 and found that when it was treated with TFA in water it underwent cyclisation to the macrocycle 51 in 82% yield, i.e. none of the anticipated plumarellide ring system 47 was obtained.  

The structure 51 is thought to arise via an intramolecular [4+2] cycloaddition from the enedione tautomers 48/49 of the hemiketal intermediate 46 (Scheme 9). Clearly the specific aqueous acid conditions we used with 45 drove the equilibrium between 46 and 48 towards the latter. By inference therefore, if we are to realise the conversion of the presumed intermediate 6 into plumarellide in vitro, then detailed attention to the nature of any catalyst and reaction conditions will need to
be addressed beforehand to avoid tautomerism to its enedione tautomer leading to unwanted side products. Of course and by contrast, an enzyme mediated cyclisation would not experience the same restrictions on tautomerism and conformational requirements of the substrate 46.

Figure 5. Free energy profile for stepwise cyclisation of the furanoxonium ion 20. Bond lengths (Å) shown are for the new bonds formed.

Figure 6. Free energy profile for acid catalysed cyclisation of the cyclic hemiketal 39. Bond lengths (Å) shown are for the new bonds formed.

Figure 7. Free energy profile for the concerted [4+2] cycloaddition of the cyclic hemiketal 39. Bond lengths (Å) shown are for the new bonds formed.
Conclusions

In conclusion, DFT calculations on potential pathways for formation of the tetracycles 12 and 17 and the pentacycle 15 suggest that furanoxonium ion intermediates could be involved. They also predict that stepwise cyclisations would be diastereoselective and favour the products observed. These results are consistent with related studies involving intermolecular reactions between furanoxonium ions and 1,3-dienes, thereby suggesting that the qualitative outcome of related cycloadditions could be predicted using this approach.

Acknowledgements

We thank The University of Nottingham and other sponsors for financial support.

Notes and references

4 All calculations apart from gCPvD3 corrections were carried out using Gaussian 09 revB.01. Default settings were used except that the UltraFine integration grid was used for calculations involving BMK and M06-2X. Initial structure searches were performed using B3LYP/6-31G(d), and all resulting structures were further optimized at the B3LYP/6-31+G(d,p) level of theory. Selected structures were also optimized using M06-2X/6-31+G(d,p) in order to confirm that representative geometries had been produced using B3LYP/6-31+G(d,p). BMK/6-311+G(d,p)//B3LYP/6-31+G(d,p) free energy corrections were applied to B3LYP/6-31G(d) free energies. Transition-state structures were all characterized by a single imaginary vibrational frequency, and intrinsic reaction coordinate (IRC) calculations were performed to confirm they connected to the appropriate energy minima. gCP-D3 corrections were applied to B3LYP/6-31G(d) energies using the gCP-D3 Webservice.

12 In principle there are four additional cyclisation modes that are possible, but these would lead to a highly strained trans-fused bicyclo[3.3.0] ring system.

Scheme 9. Formation of the polycycle 51 in preference to the plumarellide ring system 47 from the acid-catalysed rearrangement of the acetonide 45.


