Intramolecular cyclization of β-nitroso-o-quinone methides. A theoretical endoscopy of a potentially useful innate ‘reclusive’ reaction

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Oxidatively generated β-nitroso-o-quinone methides undergo an o- and/or peri-intramolecular cyclization to arene-fused 1,2-oxazoles, 1,2-oxazines or indoles. The reaction, found to be an innate process, has been scrutinized by DFT/B3LYP and MP2 calculations. Due to its rapidity, the process has been termed a ‘reclusive’ one. Competing o-(1,5)- and peri-(1,6)- or (1,5)-cyclizations advance via successive transition states. Activation barriers are drastically lowered in AcOH, probably through H hopping or tunnelling whereas they are barely reduced in other solvents. Aromaticity indices, such as HOMA, Iα, and ABO, have been used to assess the stability of the end-heterocycles and the preponderance of any one of them. Thus, the preferred cyclization mode, that is, the prevalence or exclusive formation of one of the heterocycles, appears to be oxidant-directed rather than determined by the quinone methide geometry. The question of the peri-cyclization, being a primary or a secondary process, has been tackled.

1. Introduction
o-Quinone Methides (o-QM) I (Fig. 1) have enjoyed considerable attention in organic and bioorganic synthesis as reactive intermediates. They have been invoked in biological processes, enzyme inhibition, natural product synthesis and polymer synthesis, such as melanin and lignin.1–3 Lately, there has been a resurgence of interest in their chemistry4–7 and biology.8,9 They play a key role in the chemistry of several classes of antibiotics9 and antitumour drugs.9,10 As highly polarized species, they react with electrophiles12 and nucleophiles.13–15 The latter is the most commonly used and it is usually driven by the re-aromatization of the structure. They are also known to act as DNA alkylating or cross-linking agents.15 DFT calculations have been reported with sulfur, nitrogen and oxygen nucleophiles.10 Consequently, many efforts have been directed towards understanding their properties and reaction mechanisms17 while many approaches have been devised to generate their structure.2–4,18,19 I cannot be easily isolated, therefore, it is commonly trapped in situ by (Hetero) Diels–Alder reactions, where I acts as the (hetero) diene.20,21 The reactions are exceptionally facile, compared with their traditional variants, owing to the transition state and product stabilization provided by the extended π-system.22 Early computational studies on the parent structure1,2 as well as some recent DFT-based ones,23,24 have focused on deciphering its reactivity as a Diels–Alder component or its biological activity as a Michael acceptor, in aqueous media.25–27

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Fig. 1. Structures of o-quinone methides 1, 2 and β-nitroso-o-quinone methides 3 and 4 (in the Z and E conformers, the NO group is towards and away from the carbonyl O atom, respectively. E is distinguished as E1 or E2 if the nitroso O atom is towards or away from the ring).
Conjugated $\beta$-nitrosoalkenes,\textsuperscript{28–32} a class of reactive molecules, are of significant synthetic potential and are mainly known as 2π or 4π components in cycloaddition reactions. They have been identified by isolation (in some cases, at least),\textsuperscript{33} spectroscopic characterization\textsuperscript{34} or studies of their kinetics and stereo-chemistry.\textsuperscript{35} In general, they are unstable but their stability increases markedly by halogen, aryl or $t$-alkyl substituents, strong intramolecular H-bonding\textsuperscript{36} or formation of transition metal complexes.\textsuperscript{37} These molecules are trapped by reactions similar to those of 1.\textsuperscript{28–32} A substantial part of their chemistry has been unveiled by Gilchrist\textsuperscript{38,39} and Reissig.\textsuperscript{40,41} The nitrosoalkene motif has been extensively studied in the $N$-oxide chemistry of furazans\textsuperscript{42} and has also been invoked in the formation of $N$-oxides of 1,2-benzisoxazoles.\textsuperscript{42,43} $\beta$-Nitroso-$\alpha$-quinone methides 3 or 4 (Fig. 1) encompass both 1 and 2 entities. In our earlier reports, they have been proposed as transiently generated during the oxidation of $\alpha$-hydroxyaryl acyloximes.\textsuperscript{42–45} A theoretical insight into the salient features of the structure of 3 and 4 (all its isomers) and the reflection upon their reactivity profile has been recently reported.\textsuperscript{30} Many useful heterocyclic structures have been and can be prepared from these intermediates, fused 1,2-oxazoles 9 or 10 and 1,2-oxazines 12 among them (Scheme 1). 1,2-Oxazoles, C-3 substituted with pharmacophores, is an area of intense research driven by diverse pharmaceutical applications.\textsuperscript{47} The 1,2-oxazole ring, for instance, occupies a prominent position in isoxazole-based marketed drugs, such as, penicillin antibiotics (cloxacillin, dicloxacillin, flucloxacin), antipsychotics (risperidone, paliperidone), COX 2 inhibitors (parecoxib) to name a few.

![Diagram](image.png)

Scheme 1. $\alpha$- and peri-Cyclization of oxime 5 or 6 Z/E isomers, through 7 or 8 and $\beta$-nitroso-$\alpha$-quinone methides 3 or 4.

It is known that heterocycles with a ring N–O bond are important core structures in many pharmaceuticals. Furthermore, ring opening of these heterocycles, asymmetric reduction in particular, provides access to optically active structures, core components in a variety of medicines.\textsuperscript{38} Indeed, facile ring cleavage of 1,2-oxazine 12\textsuperscript{41,44} or 1,2-oxazole 9\textsuperscript{49} lead to chemically and biologically useful outcomes, for instance ring hydroxylation\textsuperscript{43,44} or
diaryl amines as perspective metal ion chelating ligands. It is, thus, the documented significance of 1 (or 2) and the potential of their nitroso analogues 3 (or 4) as key intermediates or that of 9 and 12 in (bio)organic synthesis and biology, outlined above, along with some intriguing experimental data,\textsuperscript{44,45} that sparked the present theoretical insight into the pathways of their innate intramolecular reactivity profile.

2. Methodology

The cyclization modes of 3 and 4 were studied in the gas phase and in solution (THF, CH\textsubscript{2}Cl\textsubscript{2}). AcOH is liberated from the oxidants during the reaction, thus, the latter was studied in the presence of AcOH; AcOH was included in the calculations of stable structures of all minima, intermediates and transition states (see Fig. 2). Minima of intermediates and transition states for tentative pathways were fully optimized using the hybrid B3LYP functional\textsuperscript{50,51} coupled with the 6-311G\textsuperscript{+}+(d,p).\textsuperscript{52} However, while the suitability of the B3LYP functional has been questioned, it has, in many cases, been found reliable for theoretical calculations\textsuperscript{23–36} and prediction of organic reaction mechanisms.\textsuperscript{27} Thus, for comparison, additional calculations were carried out for some minima and their intermediate transition states using the aug-cc-pVTZ\textsuperscript{28} basis sets. The credibility of the B3LYP functional was tested using the M06-2X\textsuperscript{59} functional (recommended for the study of non-covalent interactions) (Table 1). The second order Møller\textendash Plesset perturbation theory (MP2) was also used. Relative energies, geometries and harmonic frequencies were also determined for C-3 substituted derivatives (R\textendash H, Me, Et, Ph).

Our calculations show that all three B3LYP, M06-2X and MP2 methodologies give similar geometries. Moreover, they predict similar transition energies and comparable relative energy levels irrespective of the basis set used (Table 1). A larger energy barrier and a more stabilized product was calculated for 4E\textsuperscript{+}\textsuperscript{1}→11 reaction (Fig. 4) by the M06-2X functional compared to B3LYP and MP2 techniques; whereas all three techniques gave similar energy barriers and reaction energies for the 17−12 reaction (Fig. 4). Clearly, within the same method, both basis sets, 6-311G\textsuperscript{+}+(d,p) and aug-cc-pVTZ\textsuperscript{28}, give comparable results as do the B3LYP functional with the ab initio MP2 method. It is, thus, safe to consider B3LYP/6-311G\textsuperscript{+}+(d,p), as a good choice for our purpose.

For the calculations in THF and CH\textsubscript{2}Cl\textsubscript{2} solvents, the polarizable continuum model was employed.\textsuperscript{53} This model is divided into a solute part, lying inside a cavity, surrounded by the solvent part represented as a structureless material characterized by its macroscopic properties, that is, dielectric constants and solvent radius. This method reproduces solvent effects quite well.\textsuperscript{50} For some minima and transition states, their fully optimized geometries in these solvents were found practically identical to those in the gas phase. Hence, single point calculations were carried out at the gas phase geometry for all minima and transition states.

For the calculations with AcOH, the basis set superposition error (BSSE) has been taken into account\textsuperscript{47} assuming weak hydrogen bonds among the species formed during the various stages of the reaction. Harmonic frequencies, performed using the Gaussian 09 program package,\textsuperscript{62} confirmed that the structures are minima or transition states. All calculated minima and transition structures, for R\textendash H, Me, Et and Ph, their absolute energies, relative energies and geometries in the gas phase, in THF and CH\textsubscript{2}Cl\textsubscript{2} are given in the Supplementary data section, Fig. 1S. For R\textendash H in the presence of AcOH, the calculated minima and transition structures are given in Fig. 2 and Fig. 2S, where some additional local minima are presented for some structures.

Reformulated HOMA (rHOMA), bond uniformity (I\textsubscript{A}) and average bond order/bond order deviation (ABO/BOD) have been calculated as aromaticity indices, to assess relative stabilities of the heterocycles. Reformulated HOMA (rHOMA) index\textsuperscript{63–65} has been calculated by the delineated equation:

\[
\text{rHOMA} = 1 - \frac{\alpha}{n} \sum_{i=1}^{n} \left( R_{\text{opt}} - R_i \right)^2
\]

where \(n\) is the number of bonds in the aromatic system, \(R_{\text{opt}}\) is the optimum bond length, and \(R_i\) is the real bond length of the \(i\) bond taken into consideration. This equation necessitates the use of the normalization constant \(\alpha\) for each type of bond. The used values are \(\alpha_{\text{CC}}=257.7\) and \(R_{\text{opt}}=1.388\) for CC, \(\alpha_{\text{CN}}=93.52\) and \(R_{\text{opt}}=1.334\) for CN, \(\alpha_{\text{CO}}=157.38\) and \(R_{\text{opt}}=1.265\) for CO, \(\alpha_{\text{NO}}=57.21\) and \(R_{\text{opt}}=1.248\) for NO.\textsuperscript{55}

Bond order uniformity index \(I_{\text{A}}\)\textsuperscript{56,67} and average bond order (ABO) and its deviation (BOD) from ABO index\textsuperscript{38,70} are statistical estimates of bond order variations. \(I_{\text{A}}\) index is based upon a statistical evaluation of the extent of variation of ring bond order provided by the expression:

\[
I_{\text{A}} = 100\left(1 - V/V_{\text{Kr}}\right), \quad \text{where} \quad V = \frac{100}{N} \sqrt{\frac{\sum \left| N - N_{\text{opt}} \right|^2}{n}}
\]

\(N\) is the arithmetic mean of the \(n\) various ring bond orders, \(N\) is the bond order. \(V_{\text{Kr}}\) is the value of \(V\) for the corresponding non-delocalised form of the ring and \(F\) is a scaling factor.\textsuperscript{56,67}

3. Results and discussion

Features that dominate a structure invariably accompany or match those that dictate its reactivity. Pertinent to the reactivity of 3 or 4 are the exocyclic \(\beta\)-nitrosoalkane and \(\alpha\)-quinone methide entities sharing the alkene moiety.

The NO group is a known participant in electrocyclizations\textsuperscript{28–30,70} and hetero Diels\textendash Alder cycloadditions.\textsuperscript{28–30,71} In the case at hand it has a multiple engagement. As a substituent it gives rise to E- and Z-conformers of 3 and 4. For the Z conformer only one minimum is stable. As an ambident nucleophile or electrophile\textsuperscript{22,73} it may trigger intramolecular cyclization to 12 and 14 or 9 and 10 (Scheme 1). Its HOMO is a high energy antibonding combination of N and O lone pairs responsible for its nucleophilicity while orthogonal to those orbitals is a low-lying \(\pi^*\) LUMO responsible for its electrophilicity.\textsuperscript{22,73} This feature, as well as its powerful withdrawing ability, accounts for some polarization of the alkene in 3 and 4. On the other hand, their propensity to aromatize, an inherent substantial driving force, in cooperation with the NO electronic effects, leads to the innate intramolecular cyclization.

Relative energies of Z- and E-conformers of 3 and 4 have been calculated (Fig. 3 and Table 3S). 3 or 4 for the a–c derivatives (Scheme 1) appear to have their lowest energy in the E\textsubscript{2} conformation. On the other hand, it is 3d, in its Z conformation, which is of lowest energy. The 3e\textsubscript{2}→3e\textsubscript{1} and 4e\textsubscript{2}→4e\textsubscript{1} interconversions have very low energy demands of ca. 1.4–4.2 and 0.8–3.1 kcal/mol, respectively (Fig. 3). On the contrary, the 3e\textsubscript{2}→Z and 4e\textsubscript{2}→Z interconversions have substantial energy barriers of ca. 28.1–34.8 and 18.1–35.2 kcal/mol, respectively.

The energy landscape for the intramolecular o- and peri-cyclizations of the 3 and 4 minima for R=H is depicted in Figs. 3–6, with or without the AcOH-triggered interactions. That, on the other hand, for the other derivatives is depicted in Figs. 3S–6S. The barriers of all transition states and intermediates are given with respect to 3e\textsubscript{2} or 4e\textsubscript{1} conformers, to allow for comparisons between competitive mechanisms.
Fig. 2. Minima and transition structures in the o- and peri-cyclization modes of the β-nitroso-o-quinone methides 3 and 4 with AcOH; relative energies in kcal/mol with respect to the 3E1 and 4E2 minima structures, respectively.
3.1. o-(1,5)-Cyclization

o-(1,5)-Cyclization, with the NO group acting as an electrophile, takes place through the Z conformer (Scheme 1, path (iv), Fig. 3 and Fig. 3S). An insignificant elevation is observed in solution with the corresponding barriers being 0.5, 3.1 and 0.7 kcal/mol (Fig. 3S). o-Cyclization of the other derivatives of 3 and 4 occurs instantaneously as the near zero energy barrier indicates (Scheme 1, path (iv), Fig. 3S). These observations reflect the stabilizing effect of (i) benzo-fusion, (ii) solvent and (iii) substitution on the most strained bonds in fused furoxans. This bond is slightly shorter in 3, having an energy barrier in the range of 56.6–58.9 kcal/mol (Fig. 3). The N–O2 bond in 9 falls within the range 1.202–1.242 Å found in furoxans74 and it remains as short as in the NO2 group (Table 2), a feature common to heteroaromatic N-oxides.25 The ring N–O1 bond in 9 is quite stretched (ca. 1.492 Å) and compares with the most strained bonds in fused furoxans. This bond is slightly shorter in 10. The corresponding N–O1 bond length of their deoxygenated congeners is shorter by 0.07 Å (Table 2). Interestingly, the C1–O1 bond appears within a range of 1.348–1.368 Å, thus, implying some double bond character of this bond.

3.2. peri-Cyclization

peri-Cyclization (Scheme 1) to either 12 or 14 may take place through the O- (Scheme 1, path (v)) or N-site (Scheme 1, path (vi)) of the NO group, respectively. The latter may act as either an electrophile or a nucleophile. The first and key step in either path is the formation of the ring (11 or 13 in Scheme 1).

3.2.1. 1,6-Cyclization. 1,6-Cyclization to 12 occurs through the E1 conformer and may be envisaged to proceed by way of two alternative reaction paths (Scheme 1, 11). Energy requirements for their minima and transition states are depicted in Fig. 4 (via path vii) and Fig. 5 (via path viii) and in Fig. 4S (via path vii) and Fig. 5S (via path viii).

Energy barriers (reflecting the distortion of the transition state geometry) for some intermediates are quite high, for example, 17 → 12, having an energy barrier in the range of 56.6–58.9 kcal/mol (Fig. 4S). Slightly lower energy demands, in the range of 1–2 kcal/mol, are observed in CH2Cl2 and THF compared with those in the gas phase. A marked drop for the energy barriers in the presence of AcOH is generally observed. For example, for the

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**Table 1**

Relative energies (kcal/mol) of the calculated minima and transition states included in the 4E1 → 11 and 17 → 12 reactions calculated at different levels of theory, for R–H.

<table>
<thead>
<tr>
<th>Method</th>
<th>E_1</th>
<th>E_0</th>
<th>E_1 – E_0</th>
<th>E_0 – E_1</th>
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</thead>
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<tr>
<td>B3LYP/6-311+G(d,p)</td>
<td>0</td>
<td>8.3</td>
<td>–4.5</td>
<td>0</td>
</tr>
<tr>
<td>B3LYP/aug-cc-pVTZ</td>
<td>0</td>
<td>8.1</td>
<td>–5.2</td>
<td>0.1</td>
</tr>
<tr>
<td>M062X/6-311+G(d,p)</td>
<td>0.7</td>
<td>13.5</td>
<td>–6.5</td>
<td>1.1</td>
</tr>
<tr>
<td>M062X/aug-cc-pVTZ</td>
<td>0.7</td>
<td>13.1</td>
<td>–6.5</td>
<td>1.1</td>
</tr>
<tr>
<td>MP2/6-311+G(d,p)</td>
<td>7.3</td>
<td>13.1</td>
<td>–6.5</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* Minima 4, 11, 12 and 17 are depicted in Figs. 3 and 4.

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Fig. 3. Relative energies corrected for ZPE of the o-(1,5)-cyclization of 3 and 4 minima to 9 and 10 (solid black line) in the presence of AcOH (dashed line) for R–H (C atoms–gray spheres, H–white, O–red and N–blue). Note: C, H and O atoms participating in the cyclizations in this and subsequent figures, are numbered only in a way to facilitate the presentation of results and relevant discussion.

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Additional details and figures are provided in the supplementary information (Fig. 3S, Fig. 4S, Table 2).
conversion, the energy barrier is reduced by about 20 kcal/mol. The largest one, however, of ca. 39 kcal/mol is observed for the 23→12 conversion (Fig. 5). Apparently, AcOH facilitates an H transfer, taking place not only contiguously but also more interestingly through hopping or tunnelling, perhaps, as shown by the additional transition states corresponding to H transfer between non adjacent C positions (see Figs. 2, 4 and 5). This may well account for the 20 kcal/mol drop (Fig. 4) while the lower still energy demand of 39 kcal/mol transition (Fig. 5) may be regarded as the preferred one. It is to be noted that AcOH facilitates H transfers between C atoms, which are not adjacent. As a result, AcOH intervenes in the process (Fig. 4, path vii and Fig. 5, path viii). For instance, 11 is converted to 17 in two steps, via 16 (path vii), without AcOH while in the presence of AcOH, the same conversion can occur as a one-step process, via the transition state with an overall activation energy drop of 23 kcal/mol.

3.2.2. 1,5-Cyclization. 1,5-Cyclization occurs through the E2 conformer (Scheme 1, path (vi)). Energy demands for minima and transition state structures are given in Fig. 6 and Fig. 6S. The formation of the final quinonoid structure 14 may be explained on the same grounds as in 12. This is in evidence by the notably lower energy barrier to cyclization of 4b-d, in the range of ca. 5.1–6.3 kcal/mol compared with that of its parent structure 4a of ca. 15 kcal/mol, in the gas phase. The inherent ring strain in 15, a result of accumulated n-density (see earlier arguments on 9 and 10), discourages its formation, in favour of 14. It is of interest to note that substitution, once again, confers stability on 14. The reaction (total) energy for the conversion 4E2→14 is 26.8, 32.7, 33.4 and 35.6 kcal/mol for the a-e derivatives in the gas phase. A lower energy demand of 1–3 kcal/mol is observed in CH2Cl2 and THF. Again, the presence of AcOH results in a significant decrease of the energy demand by about 30 kcal/mol (see Fig. 6). As shown in Fig. 6, in the absence of AcOH, 13 is converted to 14 via 24, in a two-step process while the presence of AcOH, effects the same conversion in one-step, via the ts13–14 transition state, with an overall activation energy drop from 35 to 5 kcal/mol.

It should be noted that the diagrams for the relative energies, relative enthalpies and free Gibbs energies for the o-(1,5)-, peri-(1,6)- and (1,5)-cyclizations of 3 or 4 minima to 9, 10, 12 or 14 are similar to the relative energies corrected for ZPE depicted in Figs. 3–6.

3.3. Reflections on the cyclization profile of 3 and 4

Experimental findings on the cyclization of 3 or 4, oxidatively generated from the oximes 5 or 6, have been quite intriguing, with regard to the varying reaction outcomes. Accordingly, 3b,c and...
4a–d give the corresponding 9 and 10, respectively (Scheme 1, path (iv)) while 3a is quite temperamental, furnishing mainly hydrolysis and polymerization products.42,43 The latter is a hardly surprising result, taking note of (a) the propensity of 3a to rapid re-aromatization and (b) the C-3 unsubstituted reactive position of 9, as soon as it is formed, giving rise to other, alternative to cyclization, competing reactions. An analogous primary o-cyclization is shown by 4a. In that case, however, benzo-fusion (a) confers
stabilization and (b) offers alternative peri-cyclization routes (Scheme 1, paths (v) and (vi)).

Lead (IV) acetate (LTA) oxidation of oximes 5 or 6 produces both 12 and 14\(^\text{14}\) while the use of phenyl iodidocacetate (PIDA) as oxidant, under similar conditions, directs the reaction selectively to 12, 43–45.\(^\text{15}\) Worth noting is that the reaction proceeds equally well in solvents of varying polarity, for example, THF, CH\(_2\)Cl\(_2\) mainly but also in MeCN.

This oxidant-selective outcome may be correlated to the O–X bond dissociation enthalpy in the transient complexes 7 or 8 (Scheme 1).\(^\text{16}\) The easier the O–X rupture, the faster will be the cyclization of the resulting intermediates 3 or 4 to the corresponding N-oxides 9, 10 or 1.2-oxazine 12. Indeed, bond dissociation enthalpies of ca. 91.17 and ca. 55.60 kcal/mol have been reported for Pb–O and I–O in various compounds.\(^\text{31}\) The notably stronger former bond, of an estimated length of ca. 2.25–2.30 Å, probably attributed to a multiple back-bonding from Pb lone pairs\(^\text{31}\) is apparently the toughest to cleave. Accordingly, of the corresponding complexes 7 or 8, the Pb-based ones have the highest energy demands for cyclization. An energy demanding six-membered pseudo chelate ring structure for these complexes may also be regarded as a viable possibility. The experimental outcomes are, indeed, consistent with these arguments.

Both oxidants release acetic acid during the reaction, regardless of the solvent used, unless it is trapped. Thus, the overall process is, in effect, dominantly acid-catalyzed by way of a 1.5-electrocyclization of 3 or 4 to 9 or 10\(^\text{13,44}\) or a 1.6 (5)-electrocyclization and sequential H shifts to 14 and/or 12\(^\text{1,2}\) (Scheme 1). The latter may be affected by hydrogen scrambling (a) intramolecularly, via a trajectory of successive shifts or (b) intermolecularly, via either acid-or solvent-assisted proton shuttling.\(^\text{83,84}\) It is the trajectory mode of the successive H shifts that determines the steric balance between the two paths.

H transfer (polar or radical in nature), an arguably important process in chemistry and biology, is usually fast but it can become rate determining if catalyzed. This is especially true when the transfer is to and from C atoms or concerted bond cleavage and formation among heavy atoms (i.e., non H atoms).

H transfer, in our case, does not necessarily impart a kinetic advantage towards stabilizing the transition states, it rather complements the thermodynamic driving force, through re-aromatization, to the end-products. The latter, perhaps, may side-step the formation of charged intermediates.

Given that the activation energy is inversely related to the solvent dielectric constant,\(^\text{45}\) the insignificant drop of the activation barriers, in the range of 1–3 kcal/mol, in other solvents, may be indicative of a rather negligible sensitivity of the reaction path to solvent polarity. Yet, this observation cannot still firmly point to the identity of the engaged species (be that dipolar, diradical or neutral).

HOMA, \(I_x\) and ABO/BOD indices have been chosen as the most responsive to the observed outcomes. Calculated HOMA values (Table 3) are consistent with a massive revert-to-type process to the extent of 81–95%. Comparing, however, the overall aromaticity change in the reaction sequences (Scheme 1), a substantial decrease is evident in the fused heterocycles 9, 10, 12, and 14. A drop in the range of 23–51% is estimated in going from the oximes 5 and 6 to 9, 10, 12 or 14. Certain features are of particular interest (a) the generation of o-quinone methide intermediates 3 and 4 is accompanied by a rise of 23% and 7%, respectively, followed by a ca. 28% drop towards the products, (b) the reaction coordinate encompasses successive transition states,\(^\text{36}\) activation barriers being due to their geometry distortion, (c) the aromatic character of 9 and 10 compares well with that of 12, (d) 10 shows a markedly lower aromatic character against 15, (e) peri (1.8)-fusion appears to increase the diene geometry of the tricycles 12 and 14, (f) a naphthalene-based peri-fused tricycle 12 appears to have an aromatic character of comparable magnitude to a quinonoid tricycle, like 14, of distinct diene geometry, (g) 15, with a higher aromatic ‘arrangement’ than the rest, cannot survive due to the severe strain inherent in the five-membered peri (1.8)-fused ring exacerbated by the N–O dipole-induced accumulated ring π-density.

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<th>(I_x)</th>
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<td>(E_2)</td>
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<tr>
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<tr>
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<th>(^d)</th>
<th>B3LYP/6-311G+(d,p).</th>
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<td>(^f)</td>
<td>Ref. 45.</td>
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<td>(^i)</td>
<td>Insignificantly low value.</td>
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</tbody>
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Compounds 3 and 4, in their Z conformation, show higher HOMA values than their precursor oximes 5 and 6, respectively (Table 3). Geometry optimization has demonstrated the development of an extended π delocalization into a five-membered N-oxide ring, through \(\text{o}-(1.5)\)-cyclization.\(^\text{46}\) The end-products N-oxides 9 and 10, on the other hand, indicate markedly lower HOMA values. The extent of delocalization, gradually building up along the reaction path, reaching the successive transition states, subsequently descends towards the end product. It is the N–O dipole, in the latter that has been incriminated for this change.\(^\text{87}\) The issues of stabilization through resonance or extended conjugation are in effect, herein. Indeed, 12 and 14 have HOMA values of comparable magnitude (Table 3). Apparently both have an inherent extended diene character, as their common stabilizing factor, of different origin, nonetheless, that is, localized π frames due to peri-fusion in 12, and benzo-fused quinone type in 14.

Bond uniformity \(I_x\) and bond order ABO/BOD variations (Table 3) follow, in general, the HOMA portrait. Accordingly, the aromatic character increases in going from the N-oxides 9 and 10 to the peri-fused 12, 14 and the fictitious 15, in concert with a corresponding increase of their diene character. The only discordance is the reverse order of magnitude among the HOMA and \(I_x\) of 12 and 14.

In as much as aromaticity reflects stability one expects that the former lags behind bonding changes at the transition states (in other words, its loss or drop should be ahead of these changes) leading to an increase of \(\Delta G\) along the reaction path. Interestingly, a benzo-fused quinone stabilization in 14 (an optimal orbital alignment, perhaps?) could be similarly accounted for a comparable \(\Delta G\) increase in the corresponding reaction path. In both cases, aromaticity changes of transition structures, as the reaction progresses, are confirmed from the bond length changes of the quinone and the nitrosoalkene entities (Tables 45–75).

Substitution also introduces selectivity in the reaction outcome (Tables 4 and 5). What is more interesting is that substitution follows the pattern observed for oxidant selectivity. Indeed, oxidation of oximes 6b–d with PIDA leads selectively to 12d or 10b, c, i.e., alkyl substitution favours \(\text{o}\)-cyclization whereas aryl substitution prefers exclusively peri-(1,6)-cyclization. Oxidation with LTA, on the other hand, appears to be substituent-insensitive and leads to both 12 and 10 in a 3:2 ratio.
It is, therefore, clear that 1,6-cyclization competes with its 1,5-rivals, in terms of geometry and energy constraints of the process. Relative energies of both o- and peri-cyclization modes suggest that 12 and 14 have comparable stabilities (Tables 4 and 5), indicating a stability order 12 > 14 > 9 > 10. We observe an overall stabilization of the reaction, up to 3 kcal/mol, in AcOH (see Tables 4 and 5) while this catalyst has a marked stabilizing effect on the minima or transition states (Fig. 5, 5, 23–25 or Fig. 6, 5, 24–25) (see also Sections 3.2.1 and 3.2.2 earlier).

From the data at hand and their analysis the following question is inevitably raised: ‘is peri-anneihilation to 12 or 14 a primary or a secondary process?’ That is, does 4 assume the E conformation directly, as soon as it is generated (primary process) or does it do it through its Z variant, o-cyclization to 10, re-opening of the latter and isomerization (secondary process)? A primary process should require that the precursor oxime (Scheme 1) takes up its E-conformation, followed by its oxidation through the complex 7 or 8 and its eventual collapse directly to 4E (E1 or E2). The Z-conformation of oxime 6a is more stable than its E-variant by 3.7 kcal/mol. The energy cost for their E-to Z-conversion is 4.2 kcal/mol. In a secondary process, on the other hand, the required Z→E conversion should go through the intermediacy of a form of 4b, eventually undergoing a peri-cyclisation. Thus, it is reasonable to assume an equilibrium among the proposed o-quinone methide forms prior to final cyclization. It is worth noting that the Z→E conversion can be envisaged through a dipolar (zwitterionic) species, such as 16 (Scheme 2). A biradical species, such as 17 (Scheme 2), on the other hand, would be consistent with some of the calculated high energy barriers (Figs. 3–6). However, the comparable barrier magnitudes calculated in solution (see earlier comments), cannot safely favour one of the possible arrangements of the intermediate species. The estimated rise in HOMA values (Table 3), during the generation of 3 and 4, lends support to an ‘aromatic’ arrangement like 16 without ruling out that of 17.

The energy barriers of these successive changes range from 12 to 16 kcal/mol, 16–32 kcal/mol and 6–9 kcal/mol, respectively. These energy costs can be supplied by the total reaction energy of ca. 38–42 kcal/mol for the most favoured reaction 4E1→12.

The reaction 4a→12 is favoured over its competitor 4a→14 by ca. 6 kcal/mol (i.e., the former has a higher total reaction energy of 39.3(40.1) kcal/mol over the latter of 33.3(35.4) kcal/mol, in the gas phase (or in solution)). Interestingly, the reactions 4b→12 and 4b→14 of the other derivatives have comparable reaction energies. However, the largest barrier in the sequence of the most favoured route of 4→12 exceeds that of 4→14 by ~10 kcal/mol. This indicates a larger distortion of the relevant transition state and is consistent with the observed much longer time taken for the cyclization reaction to be completed.

The N–O bond compressed among accumulated π-density of a distorted ring is seriously weakened and suffers facile rupture, when triggered. It is the lability of H-3 in 9 or 10 that provides that trigger. The isoxazole ring, once opened, may revert to its Z precursor or change into its E counterpart (Scheme 2), eventually undergoing a peri-cyclisation. Thus, it is reasonable to assume an equilibrium among the proposed o-quinone methide forms prior to final cyclization. It is worth noting that the Z→E conversion can be envisaged through a dipolar (zwitterionic) species, such as 16 (Scheme 2). A biradical species, such as 17 (Scheme 2), on the other hand, would be consistent with some of the calculated high energy barriers (Figs. 3–6). However, the comparable barrier magnitudes calculated in solution (see earlier comments), cannot safely favour one of the possible arrangements of the intermediate species. The estimated rise in HOMA values (Table 3), during the generation of 3 and 4, lends support to an ‘aromatic’ arrangement like 16 without ruling out that of 17.

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that takes precedence over any other that could compete through the presence of a nucleophile. The term ‘reclusive’ is, therefore, coined to identify its uniqueness.

4. Conclusions

The intramolecular cyclization of 3 and 4 is a reclusive process in that it takes precedence over any other from external stimuli. It follows an oxidant-dependent 1,6- or a competing 1,5-electrocyclization. This selectivity appears to be correlated to the dissociation enthalpy of the O–P or O–I bond of the P–I based intermediate complexes 7 or 8.

Regardless of the solvent used, it appears that the dominant reaction medium, unless trapped, is AcOH, liberated by both oxidants. Intramolecular or intermolecular solvent-assisted, contiguous or not, H shift trajectories, probably through hopping or tunnelling, account for the successive transition states involved and the substantial drop of activation barriers. Rather insignificant changes have been observed in other solvents, in the absence of AcOH, compared to those in the gas phase though stabilization, in all cases, was larger in solution. Thus, the proposed reaction paths, apparently, do not favour charged species.

Substitution follows the oxidant selectivity pattern. Accordingly, in PIDA, alkyl substitution prefers the α-(1,5)-cyclization to N-oxides 9 or 10 and aryl substitution favours the peri-(1,6)-cyclization to 1,2-oxazine 12. LTA, on the other hand, proves to be substituent-insensitive, giving rise to all cyclization products.

Aromaticity indices, as stability indicators of the end structures, cannot discriminate between competing paths, as their values are of comparable magnitude. They do, however, suggest a markedly lower aromaticity of the heterocycles compared to their precursors, attributed to the peri-triggered enhanced diene geometry of their π-frame.

The available evidence cannot irrefutably clarify whether the peri-cyclization is a primary or a secondary process. It appears that the preferred path is oxidant-directed.

The reaction takes precedence over any other that could compete through the presence of a nucleophile and has been termed ‘reclusive’ to identify its uniqueness.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.11.020.

References and notes

78. Lead(IV) acetate oxidation of 4 gives 12 and 14 in moderate yields and a spiro dimer as the major product (see Ref. 43). Phenyliododiacetate (PIDA) oxidation, furnishes 12 selectively (see Ref. 47). On the other hand, the oxidation can be selectively driven to the dimer, if run in AcOH/TFA or to 12 (as with PIDA) in the presence of N-morpholine oxide (NMO) (see: Rosenau, T.; Mereiter, K.; Jäger, C.; Schmidt, P.; Kosma, P. Tetrahedron 2004, 60, 5719) and Ref. 43. Same reaction outcome is obtained with Ag2O oxidant.
83. Many experimental and theoretical reports, as well as book chapters and reviews, have been devoted to Proton Transfer (PT) phenomena. Tunneling (a quantum effect of going through and not over an energy reaction barrier) (see Ref. 76) or hopping (or ‘hop-turn’ or Grätthuss mechanism) are the currently accepted proton relay modes (see also: Alkorta, I.; Elguero, J. Org. Biomol. Chem. 2006, 4, 396 and references cited therein).
88. (a) Unsubstituted 9 or 10 are not isolable, see also Ref. 79. (b) Aryl substituted 10, upon prolonged reaction, leads to 12 whereas its alkyl substituted analogues give 14: Supsana, P.; Tsoungas, P. G.; Tzeli, D.; Varvounis, G. unpublished work.