Potential for Ladderane (Bio)synthesis from Oligo-Cyclopropane Precursors

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**ABSTRACT:** Quantum chemical calculations were used to determine the energetic viability of several mechanisms for formation of ladderanes from oligocyclopropanes. Pathways involving radical cations, diradicals, and carbocations were considered, and a hybrid of carbocation and radical cation pathways was predicted to have the lowest overall barrier.

**INTRODUCTION**

Ladderanes—polycyclic molecules with two or more fused cyclobutane rings—have attracted the attention of biologists, biochemists, computational chemists, and synthetic chemists because of their unusual, highly strained, molecular skeletons. Reported methods for the laboratory synthesis of ladderanes include templated photodimerizations and several innovative target-oriented multistep syntheses. While various aspects of ladderane biosynthesis have been revealed, energetically viable, biologically relevant reactions that form ladderanes have not been characterized either experimentally or theoretically. Rattray et al. described a variety of gene candidates that might be involved in ladderane biosynthesis, and suggested that the cyclization of polyunsaturated fatty acids was unlikely to generate ladderane lipids as previously hypothesized. Mechanisms involving the polycyclization of carbocations, carbanions, and radicals derived from polyenes also were shown (using quantum chemical computations) to have barriers and endergonicities that are prohibitive.

If polyunsaturated fatty acids are not involved in ladderane biosynthesis, what alternative precursors are possible? In attempting to answer this question, we sought structural units known to be formed in nature that might themselves be strained, allowing their conversion to ladderanes to be at least approximately thermoneutral. Yes, this would pass the energetic buck, but via a hand-off to known biosynthetic chemistry. Ultimately, we arrived at the hypothesis that oligocyclopropanes might be suitable ladderane precursors. The biosynthesis of oligocyclopropanes is well-known and they have been isolated from bacteria (although not from ladderane-producing anammox bacteria). Beller and co-workers tested 34 genes putatively involved in ladderane biosynthesis in anammox bacteria and disclosed that S-adenosylmethionine (SAM)-utilizing enzymes and desaturases are present. We speculate that the former may be involved in cyclopropane formation and/or in generating reactive intermediates from cyclopropanes and the latter may be involved in creating one or more cyclobutane rings after rearrangement (Scheme 1). Here, we explore the energetic viability of oligocyclopropane-to-ladderane rearrangements using computational quantum chemistry.

**RESULTS AND DISCUSSION**

A simplified model system, 1 (Scheme 2), was used to investigate the transformation of a bis-cyclopropane into a ladderane. The thermodynamic feasibility of this model was first assessed at several levels of theory—all of which predict that the overall reaction should be approximately thermoneutral or slightly exergonic.

Three possible pathways connecting 1 to 2 were initially considered—one involving radical cations, one involving diradicals, and one involving carbenes. Each pathway can be divided into three key parts: ring-opening of one cyclopropane, ring-expansion of a second cyclopropane to...
form a cyclobutane ring, and ring-closure to form the second
cyclobutane ring. The radical cation pathway would be
initiated by removal of an electron. Diradical formation
might be accomplished by sufficient heat or light of an
appropriate wavelength. Carbocation generation could occur
by protonation; cyclopropanes are well-known to be more
basic than other alkanes.20,21 These steps are not treated here
because all have biological precedent.22,23 Our focus is
therefore on the feasibility of rearrangement pathways.

**Radical Cation Pathway.** Rearrangement of radical cation
3 (Figure 1) is predicted to have too high a barrier to be likely
in a biological setting.24 While barriers for initial ring-opening
and rearrangement/ring-closure are not high, ring-opening to
form 5 is predicted to be endergonic by >10 kcal mol\(^{-1}\),
making the overall barrier to form 7 > 30 kcal mol\(^{-1}\). We
considered the possibility that this barrier could be lowered by
CH\(^{-}\)X hydrogen-bonding.25–29 An electrostatic potential map
for TSS\(^6\) indicates that a positive charge is largely localized on
the migrating H\(^{-}\)C group (Figure 2, left). We located a TSS,
8, with the lone pair of an ammonia molecule (a crude model
of an enzyme residue that can accept a hydrogen-bond 30)
pointing at the H\(^{-}\)C group (Figure 2, right). This arrangement
does lower the barrier, but not by enough. While we cannot
rule out the possibility that a more suitable enzyme pocket could selectively bind TSS \(^6\) to a greater extent, we suspect
that the approximately 10 kcal mol\(^{-1}\) of selective binding energy necessary is not likely to be accessible, given the dearth
of additional binding handles on TSS \(^6\).

**Diradical Pathways.** Thermal generation of a singlet
diradical is expected to be unlikely, given the strengths of
bonds in cyclopropanes.31,32 This expectation is borne out by
our computations (Figure 3), but bond-breaking and ring
expansion appear to be concerted (via TSS \(^9\)). Simple bond
cleavage would be expected to result in a cyclopropylcarbinyl
radical substructure. Barriers for ring opening of these to
homoallylic radicals are notoriously low,33 but not zero, so not
only was our failure to locate the expected intermediate
surprising, so was the observation that initial ring opening is
merged with ring expansion rather than cleavage. Nonetheless,
this process has a prohibitively high barrier.

We also considered rearrangement of a triplet diradical,
which, although unlikely, could arise via photochemical activation.34 Triplet diradical 12 (Figure 4) was obtained as a
minimum, but rearrangement of the type observed for the
singlet diradical (via TSS \(^9\), Figure 4, red; cf. TSS \(^9\), Figure 3)
is associated with a barrier of nearly 50 kcal mol\(^{-1}\). This barrier
is again prohibitively high. In addition, its magnitude suggests
that approximately half of the 1-to-9 barrier is associated with
rearrangement and half with thermal bond cleavage. Because the singlet analog of diradical 12 was not located as a minimum, its two radical centers must not be fully disjoint.35 Because we located diradical 12 as a minimum, we were able to examine an alternative pathway involving the expected cyclopropylcarbiny1-to-homolytic radical cleavage (Figure 4, blue). While this cleavage reaction does indeed have a low barrier (<10 kcal mol−1) and is exergonic, subsequent ring closure to form diradical 17 is predicted to be associated with a barrier of >30 kcal mol−1. In sum, we have found no viable diradical pathway.

Carbocation Pathway. Carbocation formation from a bis-cyclopropane requires protonation. Here, we use NH4+ as a simple proton source only, not as a commitment to protonated lysine as a biological proton source. Edge protonation of one cyclopropane ring of 1 is predicted to proceed with a low barrier (18 → 19 → 20, Figure 5). Subsequent ring expansion is coupled to migration of the conjugate base, NH3 (bound by CH–N interactions), and is predicted to have a barrier of 26–29 kcal mol−1. This barrier is high for a biological reaction, but not as high as those discussed above. Reaching TSS 21 lands the system on a relatively flat portion of the potential energy surface, associated primarily with movement of the conjugate base in preparation for deprotonation.

Working Together to Win? Realizing that initial cyclopropane cleavage is facilitated by protonation, while the ring-expansion step for the radical cation reaction has a lower barrier than that for the carbocation reaction, we investigated whether these two pathways might be combined to lead to a pathway with a lower overall barrier. In that, a SAM-utilizing enzyme has been implicated in ladderane biosynthesis (vide supra), we considered the possibility that a deoxyadenosyl radical (dAdo*) could abstract a hydrogen atom from 20 (Figure 5), to give 5 (Figure 1).36 The predicted energetics for such a hybrid pathway are shown in Figure 6. Indeed, protonation/ring-opening/H-atom transfer to form 33 is predicted to have an overall barrier of ~15 kcal mol−1. As described above, radical cation ring-expansion is predicted to have a barrier of ~20 kcal mol−1 in the gas phase. The only wrinkle is that dAdo−H dissociation is predicted to be endergonic. This is eliminated when calculations are carried out in chloroform, a very crude model of the general dielectric environment of an enzyme active site (Figure 6; see the Supporting Information for solvent calculations on other mechanisms, all of which only displayed small effects).37,38 While the overall barrier en route to 33 then is raised to 24 kcal mol−1. Unfortunately, we cannot reliably estimate where the exact energies would lie an enzyme environment, although they could certainly be lowered. Note, for example, that dAdo participates in an attractive cation−π interaction39 in our model system that may not be present or could be modulated in an enzyme active site, allowing binding and dissociation energies to be tuned.

Potential Dead Ends. Although the hybrid pathway is energetically reasonable, it is accompanied by a potential problem. Radical cation 36 needs to capture an electron to form a ladderane product. Our estimate of its reduction potential (SMD(H2O)/UB2PLYP-D3(BJ)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (italics), and UCCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (bold), and UDLPNO-CCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (normal text), UDLPNO-CCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (italics) are shown in kcal mol−1; select distances are shown in Å.

Figure 3. Stationary points for the singlet diradical pathway. Relative free energies determined with UB2PLYP-D3(BJ)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (normal text), UDLNOC-CCSDD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (bold), and UCCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (italics) are shown in kcal mol−1; select distances are shown in Å.

Figure 4. Stationary points for triplet diradical pathways. Relative free energies determined with UB2PLYP-D3(BJ)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (normal text), UDLNOC-CCSDD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (bold), and UCCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (italics) are shown in kcal mol−1; select distances are shown in Å.
species such as 44 could, in principle, serve as precursors to them.

**CONCLUSIONS**

Several possible mechanisms for the conversion of oligocyclopropanes to ladderanes were explored using quantum chemical calculations. On the basis of our results, we conclude that a hybrid mechanism that combines cyclopropane activation via protonation with subsequent H-atom transfer and ring-expansion is the most reasonable, on energetic grounds, of the scenarios considered. Whether such a process will be discovered in nature is an open question, but one we hope to see answered.

**METHODS**

Geometries of stationary points were fully optimized using (U)B3LYP-D3(BJ)/Def2-TZVPP and DLPNO-CCSD(T)/cc-pVTZ//B3LYP-D3(BJ)/Def2-TZVPP (bold), and CCSD(T)/cc-pVTZ//B3LYP-D3(BJ)/Def2-TZVPP (italics) are shown in kcal mol\(^{-1}\); select distances are shown in Å.
structures in the gas phase (see the Supporting Information for results with water). Additional single-point calculations using (U)CCSD(T)/cc-pVTZ were performed on select structures to benchmark these two levels of theory (see the Supporting Information for all benchmarking data). All structures were characterized as transition-state structures (TSSs) or minima through vibrational analysis. All energies reported are Gibbs free energies at 298 K (i.e., they incorporate thermal and entropy corrections from the method used for optimization; the default RRHO approximation was used) unless stated otherwise. Structural drawings were produced with CYLview.57

Figure 7. Stationary points for transformations of 36 in gas phase. Relative free energies determined with UB2LYP-D3(BJ)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (normal text), UDLPNO-CCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (bold), and UCCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (italics) are shown in kcal mol$^{-1}$; select distances are shown in Å. While 39, a TSS for the conformational change that converts 38 to 40, is slightly lower in free energy that 38, it is slightly higher in electronic energy (not shown); the scenario occurs for TSS 41 at some levels of theory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c03735.

Single-point energy results and benchmarking; solvent effect of mechanisms; transformations of the methyl [2]-ladderane radical cation and related methyl [3]-ladderane radical cation; and coordinates and energies for computed structures (PDF)

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Notes

The authors declare no competing financial interest.
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