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Article

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

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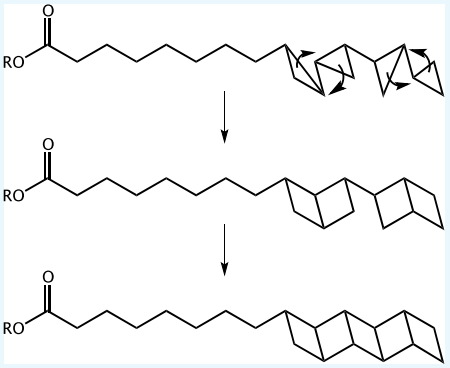
ABSTRACT: Quantum chemical calculations were used to determine the energetic viability of several mechanisms for formation of ladderanes from oligocyclopropanes. Pathways involving radical cations, diradicals, and carbocations were considered, and a hybrid of carbocation and radical cation pathways was 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.[1−16] Reported methods for the laboratory synthesis of ladderanes include templated photodimerizations[9,10] and several innovative target-oriented multistep syntheses.[8,11−13] While various aspects of ladderane biosynthesis have been revealed,[3−5] 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.[4] 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.[6,17]

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).[7] Beller and coworkers tested 34 genes putatively involved in ladderane biosynthesis in anammox bacteria and disclosed that *S*-adenosylmethionine (SAM)-utilizing enzymes and desaturases are present.[5] We speculate that the former may be involved in cyclopropane formation[18,19] 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 [2] 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 (Scheme 2)—one involving radical cations, one involving diradicals, and one involving carbocations. Each pathway can be divided into three key parts: ring-opening of one cyclopropane, ring-expansion of a second cyclopropane to

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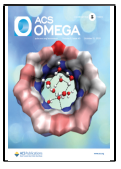

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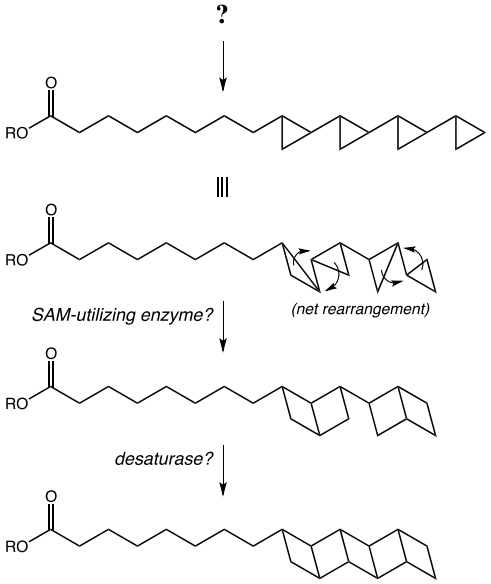
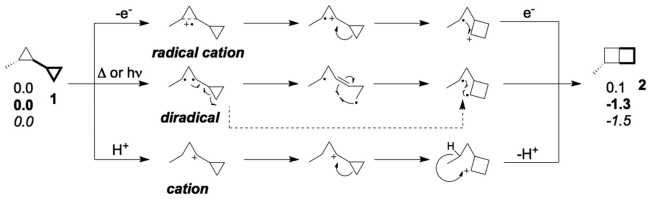
Scheme 1. Initial Hypothesis for Ladderane Biosynthesis via Oligocyclopropanes



Scheme 2. Mechanistic Pathways Considered Initially[a]



[a]Relative free energies of **1** and **2**, computed with B2PLYP-D3(BJ)/cc-pVTZ//B3LYP-D3(BJ)/Def2-TZVPP (normal text), 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}.

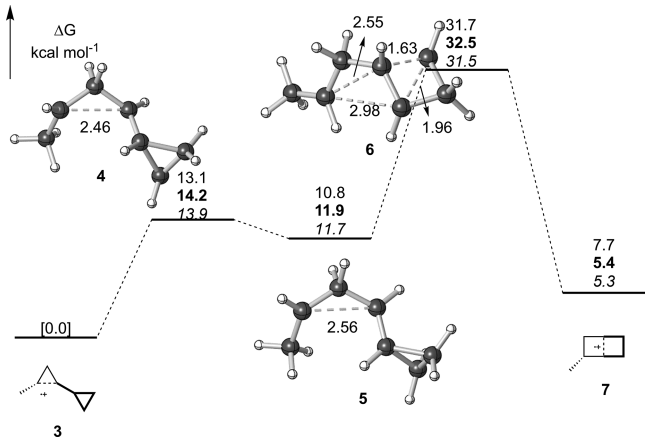


Figure 1. Stationary points for the radical cation pathway. Relative free energies determined with UB2PLYP-D3(BJ)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (normal text), UDLPNO-CCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (bold), and UCCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (italics) are shown in kcal mol^{-1}; select distances are shown in Å.

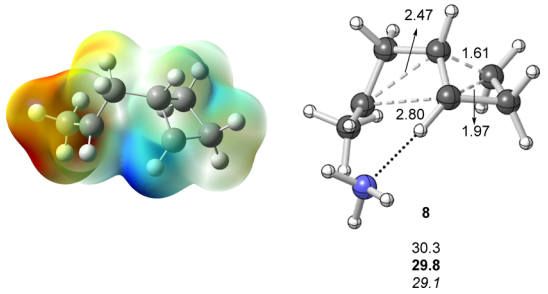


Figure 2. Electrostatic potential map of TSS **6** (left), with an isovalue = 0.004 and charge range of 0.150−0.230. TSS **8** (right). Computed overall free energies barriers are shown in kcal mol^{-1}, and select distances are shown in Å (UB2PLYP-D3(BJ)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (normal text), UDLPNO-CCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (bold), and UCCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (italics)).

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 **13**, 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

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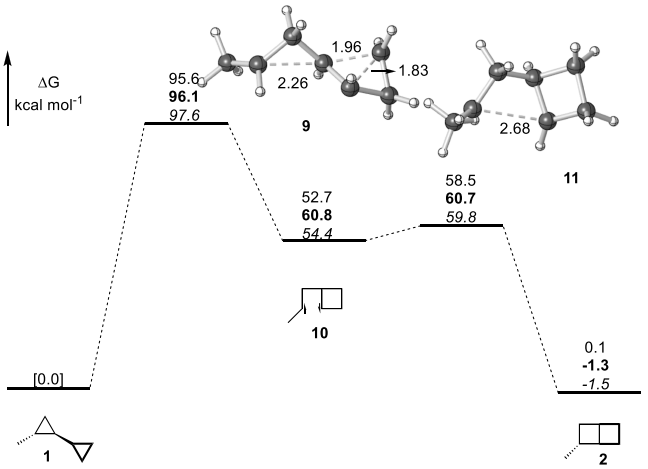

Figure 3. Stationary points for the singlet diradical pathway. Relative free energies determined with UB2PLYP-D3(BJ)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (normal text), UDLPNO-CCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (bold), and UCCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (italics) are shown in kcal mol^{-1};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

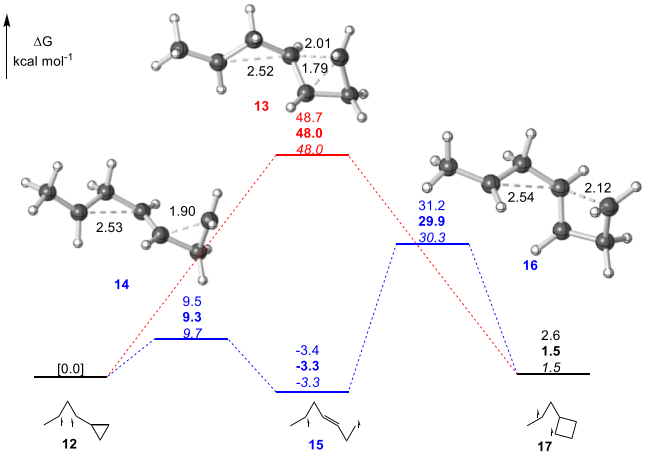

Figure 4. Stationary points for triplet diradical pathways. Relative free energies determined with UB2PLYP-D3(BJ)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (normal text), UDLPNO-CCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (bold), and UCCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (italics) are shown in kcal mol^{-1}; select distances are shown in Å.

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 cyclopropylcarbinyl-to-homoallylic 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 generation from a bis-cyclopropane requires protonation. Here, we use NH_4^+ 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, NH_3 (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$^\bullet$) 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 issue 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] but 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 interaction[39−41] 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(H_2O)/UB2PLYP-D3(BJ)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP with E_{abs}(SHE) = 4.4)[43] indicates this process is thermodynamically feasible (1.4 V, **36** → **2′**, Figure 7). However, ladderane radical cations are known to readily ring-open,[42] a process that we compute to have a very low barrier (<5 kcal/mol) for **36** (**36** → TSS **37** → **38**), in accord with experiments on related systems.[42] Although **38** cannot be readily reduced (predicted reduction potential: −1.0 V, **38** → **43**), it can undergo a conformational change from a boat-like to a chair-like structure (**38** → TSS **39** → **40**) that is predicted to be effectively barrierless.[42] Chair-like **40** can then ring-open to a hexadienyl radical cation (**42**), which can readily accept an electron (predicted reduction potential: 1.7 V, **42** → **44**). So, does this pathway represent a dead-end for the hybrid mechanism described above? It is difficult to answer this question, but what is clear is that if a ladderane radical cation is produced, conversion to chair-like structures must be prevented,[44] that is, initial ring-opening can occur because that process is likely to be reversible given the reduction potential of species such as **38**, but further ring-opening must be prevented. Note, however, that ladderane lipids containing cyclohexane rings are also known,[1−16] and

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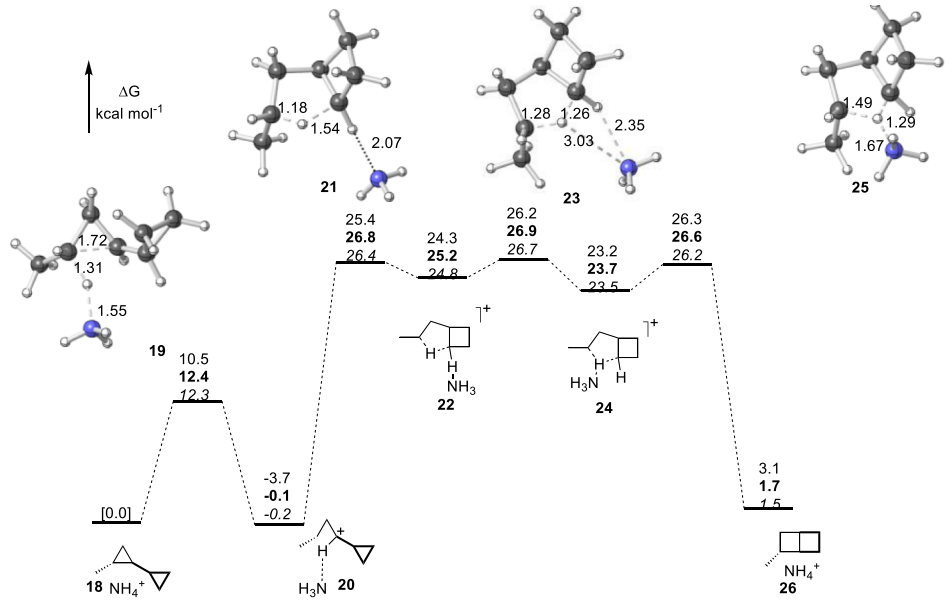

Figure 5. Stationary points for the carbocation pathway. Relative free energies determined with B2PLYP-D3(BJ)/cc-pVTZ//B3LYP-D3(BJ)/Def2-TZVPP (normal text), DLPNO-CCSD(T)/cc-pVTZ//B3LYP-D3(BJ)/Def2-TZVPP (bold), and CCSD(T)/cc-pVTZ//B3LYP-D3(BJ)/Def2-TZVPP (italics) are shown in kcal mol^{-1}; select distances are shown in Å.

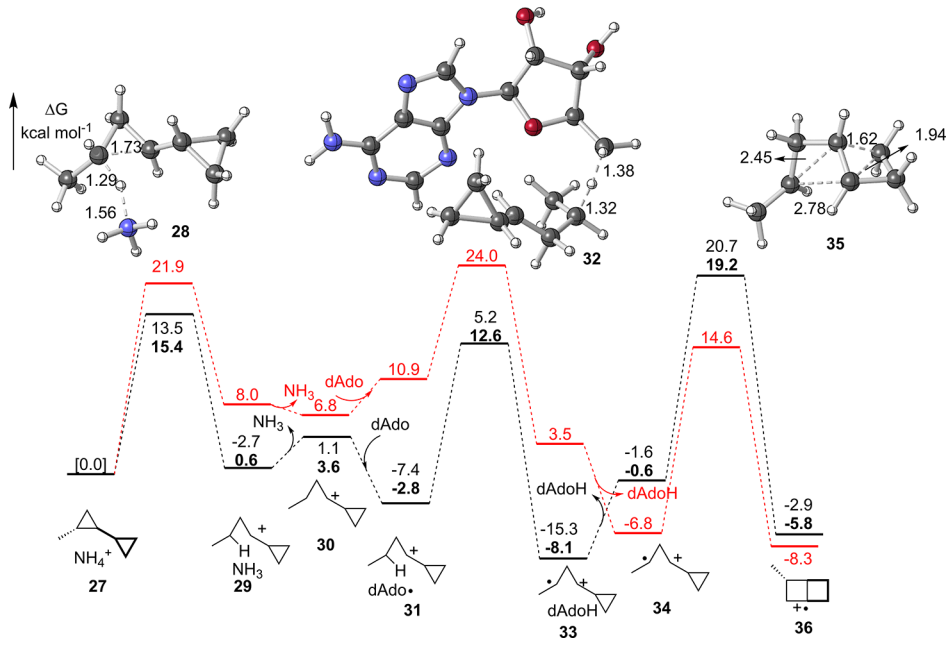

Figure 6. Stationary points for the hybrid pathway in gas phase and chloroform. Relative free energies determined with UB2PLYP-D3(BJ)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (normal text), UDLPNO-CCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (bold), and SMD-(chloroform)-UB2PLYP-D3(BJ)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (red) 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[45]/Def2-TZVPP[46] with Grimme's D3(BJ) correction[47,48] in the gas phase using the *Gaussian09* package.[49] Single-point calculations using(U)DLNPO-CCSD(T)[50]/cc-pVTZ[51] and (U)B2PLYP[52]/cc-pVTZ with D3(BJ) correction were carried out with the *ORCA 4.0*[53,54] and *Gaussian09* packages, respectively. Solvent Energies were calculated using the SMD solvation model[55] with chloroform based on the

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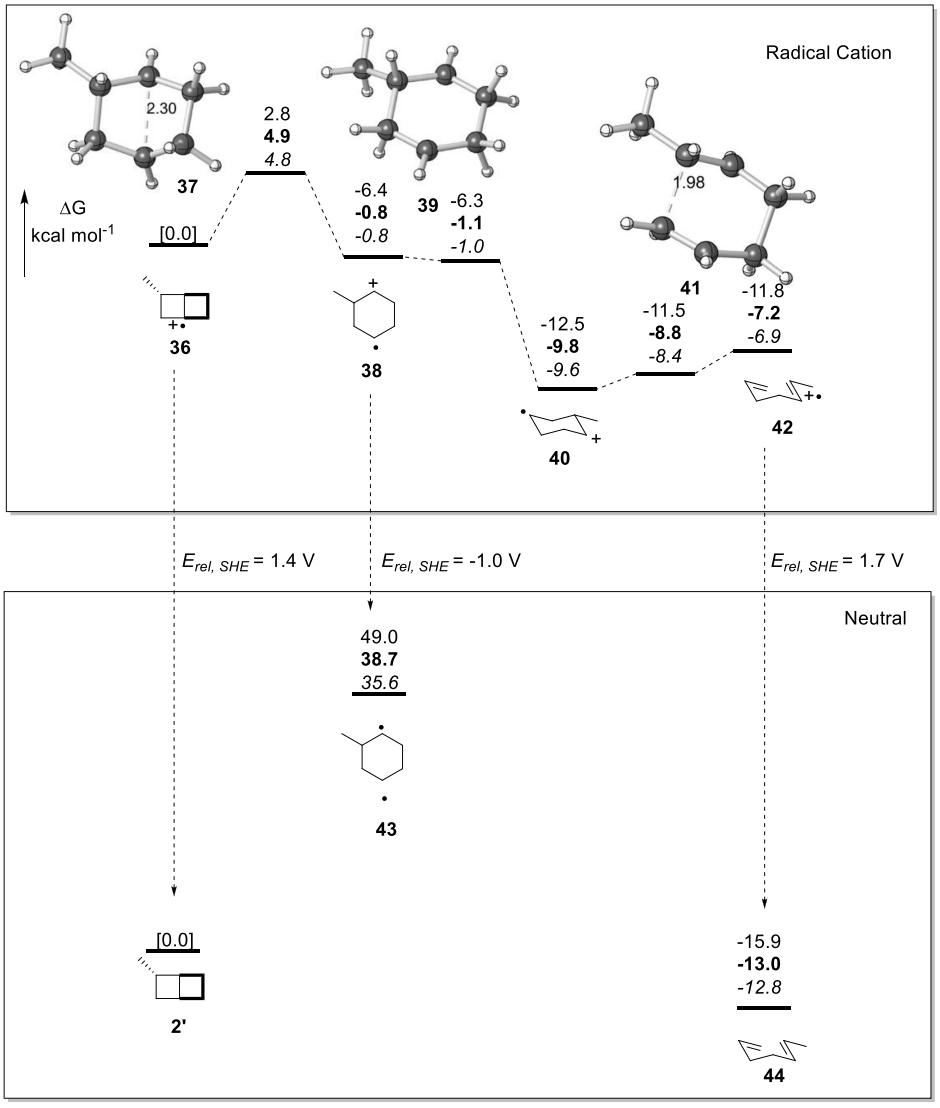

Figure 7. Stationary points for transformations of **36** in gas phase. Relative free energies determined with UB2PLYP-D3(BJ)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (normal text), UDLPNO-CCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (bold), and UCCSD(T)/cc-pVTZ//UB3LYP-D3(BJ)/Def2-TZVPP (italics) are shown in 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.

structures in the gas phase (see the Supporting Information for results with water). Additional single-point calculations using(U)CCSD(T)[56]/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]

■ 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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■ REFERENCES

(1) Miller, M. A.; Schulman, J. M. AM1, MNDO and MM2 studies of concatenated cyclobutanes: prismanes, ladderanes and asteranes. *J. Mol. Struct.: THEOCHEM* **1988**, *163*, 133−141.
(2) Novak, I. Ring Strain in [n]ladderanes. *J. Phys. Chem. A* **2008**, *112*, 10059−10063.
(3) Strous, M.; Pelletier, E.; Mangenot, S.; Rattei, T.; Lehner, A.; Taylor, M. W.; Horn, M.; Daims, H.; Bartol-Mavel, D.; Wincker, P.; Barbe, V.; Fonknechten, N.; Vallenet, D.; Segurens, B.; Schenowitz-Truong, C.; Médigue, C.; Collingro, A.; Snel, B.; Dutilh, B. E.; Op den Camp, H. J. M.; van der Drift, C.; Cirpus, I.; van de Pas-Schoonen, K. T.; Harhangi, H. R.; van Niftrik, L.; Schmid, M.; Keltjens, J.; van de Vossenberg, J.; Kartal, B.; Meier, H.; Frishman, D.; Huynen, M. A.; Mewes, H.-W.; Weissenbach, J.; Jetten, M. S. M.; Wagner, M.; Le Paslier, D. Deciphering the evolution and metabolism of an anammox bacterium from a community genome. *Nature* **2006**, *440*, 790−794.
(4) Rattray, J. E.; Strous, M.; Op den Camp, H. J.; Schouten, S.; Jetten, M. S.; Damsté, J. A comparative genomics study of genetic products potentially encoding ladderane lipid biosynthesis. *Biol. Direct* **2009**, *4*, 8.
(5) Javidpour, P.; Deutsch, S.; Mutalik, V. K.; Hillson, N. J.; Petzold, C. J.; Keasling, J. D.; Beller, H. R. Investigation of Proposed Ladderane Biosynthetic Genes from Anammox Bacteria by Heterologous Expression in E. coli. *PLoS One* **2016**, *11*, e0151087.
(6) Nouri, D. H.; Tantillo, D. J. Attack of radicals and protons on ladderane lipids: quantum chemical calculations and biological implications. *Org. Biomol. Chem.* **2012**, *10*, 5514.
(7) Wessjohann, L. A.; Brandt, W.; Thiemann, T. Biosynthesis and metabolism of cyclopropane rings in natural compounds. *Chem. Rev.* **2003**, *103*, 1625−1648.
(8) Mercer, J. A. M.; Cohen, C. M.; Shuken, S. R.; Wagner, A. M.; Smith, M. W.; Moss, F. R.; Smith, M. D.; Vahala, R.; Gonzalez-Martinez, A.; Boxer, S. G.; Burns, N. Z. Chemical synthesis and self-assembly of a ladderane phospholipid. *J. Am. Chem. Soc.* **2016**, *138*, 15845−15848.
(9) Hopf, H.; Greiving, H.; Jones, P. G.; Bubenitschek, P. Topochemical reaction control in solution. *Angew. Chem., Int. Ed.* **1995**, *34*, 685−687.
(10) Gao, X.; Friščić, T.; MacGillivray, L. R. Supramolecular Construction of Molecular Ladders in the Solid State. *Angew. Chem., Int. Ed.* **2003**, *43*, 232−236.
(11) Mascitti, V.; Corey, E. J. Total Synthesis of (±)-Pentacycloanammoxic Acid. *J. Am. Chem. Soc.* **2004**, *126*, 15664−15665.
(12) Mascitti, V.; Corey, E. J. Enantioselective synthesis of pentacycloanammoxic acid. *J. Am. Chem. Soc.* **2006**, *128*, 3118−3119.
(13) Hancock, E. N.; Kuker, E. L.; Tantillo, D. J.; Brown, M. K. Lessons in Strain and Stability: Enantioselective Synthesis of (+)-[5]-Ladderanoic Acid. *Angew. Chem.* **2020**, *132*, 444−449.
(14) Hopf, H.; Greiving, H.; Beck, C.; Dix, I.; Jones, P. G.; Desvergne, J.-P.; Bouas-Laurent, H. One-Pot Preparation of [n]-Ladderanes by [2? + 2?] Photocycloaddition. *Eur. J. Org. Chem.* **2005**, 567−581.
(15) Nouri, D.; Tantillo, D. They came from the deep: Syntheses, applications, and biology of ladderanes. *Curr. Org. Chem.* **2006**, *10*, 2055−2074.
(16) Hopf, H. Step by Step-From Nonnatural to Biological Molecular Ladders. *Angew. Chem., Int. Ed.* **2003**, *42*, 2822−2825.
(17) Nouri, D. H. Ph.D. Dissertation, UC Davis, 2007.
(18) Kuo, M. S.; Zielinski, R. J.; Cialdella, J. I.; Marschke, C. K.; Dupuis, M. J.; Li, G. P.; Kloosterman, D. A.; Spilman, C. H.; Marshall, V. P. Discovery, isolation, structure elucidation, and biosynthesis of U-106305, a cholesteryl ester transfer protein inhibitor from UC 11136. *J. Am. Chem. Soc.* **1995**, *117*, 10629−10634.
(19) Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams, D. J. Iterative cyclopropanation: a concise strategy for the total synthesis of the hexacyclopropane cholesteryl ester transfer protein inhibitor U-106305. *J. Am. Chem. Soc.* **1997**, *119*, 8608−8615.
(20) Battiste, M. A.; Coxon, J. M. *Cyclopropyl Group Volume 1 and Volume 2*; John Wiley & Sons, Ltd: Chichester, U.K., 1987; pp 255−305.
(21) Wiberg, K. B.; Kass, S. R. Electrophilic cleavage of cyclopropanes. Acetolysis of alkylcyclopropanes. *J. Am. Chem. Soc.* **1985**, *107*, 988−995.
(22) Rahier, A.; Benveniste, P.; Cattel, L. In vitro incorporation of2H at the C-10 methyl group of obtusifoliol during the enzymatic cleavage of the 9*β*,19*β*-cyclopropane ring of cycloeucalenol. *J. Chem. Soc., Chem. Commun.* **1976**, 287−288.
(23) Rahier, A.; Cattel, L.; Benveniste, P. Mechanism of the enzymatic cleavage of the 9*β*,19-cyclopropane ring of cycloeucalenol. *Phytochemistry* **1977**, *16*, 1187−1192.
(24) Wang, S. C.; Tantillo, D. J. Theoretical Studies on Synthetic and Biosynthetic Oxidopyrylium−Alkene Cycloadditions: Pericyclic Pathways to Intricarene. *J. Org. Chem.* **2008**, *73*, 1516−1523.
(25) Alkorta, I.; Rozas, I.; Elguero, J. Non-conventional hydrogen bonds. *Chem. Soc. Rev.* **1998**, *27*, 163−170.
(26) Desiraju, G. R. C-H···O and other weak hydrogen bonds. From crystal engineering to virtual screening. *Chem. Commun.* **2005**, 2995−3001.
(27) Calhorda, M. J. Weak hydrogen bonds: theoretical studies. *Chem. Commun.* **2000**, 801−809.
(28) Bojin, M. D.; Tantillo, D. J. Nonclassical Carbocations as C−H Hydrogen Bond Donors. *J. Phys. Chem. A* **2006**, *110*, 4810−4816.
(29) Hong, Y. J.; Tantillo, D. J. Perturbing the Structure of the 2-Norbornyl Cation through C−H···N and C−H···*π* Interactions. *J. Org. Chem.* **2007**, *72*, 8877−8881.
(30) Tantillo, D. J. How an Enzyme Might Accelerate an Intramolecular Diels−Alder Reaction: Theozymes for the Formation of Salvileucalin B. *Org. Lett.* **2010**, *12*, 1164−1167.
(31) Berson, J. A.; Pedersen, L. D.; Carpenter, B. K. Thermal stereomutation of cyclopropanes. *J. Am. Chem. Soc.* **1976**, *98*, 122−143.
(32) Dewar, M. J. S.; Dougherty, R. C. *The PMO Theory of Organic Chemistry*; Springer US: Boston, MA, 1975; Vol. *106*.
(33) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. Calibration of a new horology of fast radical clocks. Ring-opening rates for ring- and *α*-alkyl-substituted cyclopropylcarbinyl radicals and for the bicyclo[2.1.0]pent-2-yl radical. *J. Am. Chem. Soc.* **1991**, *113*, 5687−5698.
(34) Bernardi, F.; Olivucci, M.; Robb, M. A. Potential energy surface crossings in organic photochemistry. *Chem. Soc. Rev.* **1996**, *25*, 321−328.
(35) Tsuji, Y.; Hoffmann, R.; Strange, M.; Solomon, G. C. Close relation between quantum interference in molecular conductance and diradical existence. *Proc. Natl. Acad. Sci. U.S.A.* **2016**, *113*, E413−E419.
(36) Broderick, J. B.; Duffus, B. R.; Duschene, K. S.; Shepard, E. M. Radical S-Adenosylmethionine Enzymes. *Chem. Rev.* **2014**, *114*, 4229−4317.
(37) Pitera, J. W.; Falta, M.; Van Gunsteren, W. F. Dielectric properties of proteins from simulation: the effects of solvent, ligands, pH, and temperature. *Biophys. J.* **2001**, *80*, 2546−2555.
(38) Li, L.; Li, C.; Zhang, Z.; Alexov, E. On the dielectric "constant" of proteins: smooth dielectric function for macromolecular modeling and its implementation in DelPhi. *J. Chem. Theory Comput.* **2013**, *9*, 2126−2136.
(39) Ma, J. C.; Dougherty, D. A. The Cation−*π* Interaction. *Chem. Rev.* **1997**, *97*, 1303−1324.
(40) Dougherty, D. A. The Cation−*π* Interaction. *Acc. Chem. Res.* **2013**, *46*, 885−893.

https://dx.doi.org/10.1021/acsomega.0c03735
ACS Omega 2020, 5, 26134−26140

(41) Mahadevi, A. S.; Sastry, G. N. Cation−π interaction: Its role and relevance in chemistry, biology, and material science. *Chem. Rev.* **2013**, *113*, 2100−2138.
(42) Williams, F.; Guo, Q. X.; Bebout, D. C.; Carpenter, B. K. ESR evidence for the stereospecific formation of the chair cyclohexane-1, 4-diyl radical cation from both bicyclo [2.2.0] hexane and 1,5-hexadiene. *J. Am. Chem. Soc.* **1989**, *111*, 4133−4134.
(43) Marenich, A. V.; Ho, J.; Coote, M. L.; Cramer, C. J.; Truhlar, D. G. Computational electrochemistry: prediction of liquid-phase reduction potentials. *Phys. Chem. Chem. Phys.* **2014**, *16*, 15068−15106.
(44) The energetics do not change significantly for a [3] ladderane; see Supporting Information for details.
(45) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. Ab initio calculation of vibrational absorption and circular dichroism spectra using density functional force fields. *J. Phys. Chem.* **1994**, *98*, 11623−11627.
(46) Weigend, F.; Ahlrichs, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297−3305.
(47) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *J. Chem. Phys.* **2010**, *132*, 154104.
(48) Grimme, S.; Ehrlich, S.; Goerigk, L. Effect of the damping function in dispersion corrected density functional theory. *J. Comput. Chem.* **2011**, *32*, 1456−1465.
(49) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M. .; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M. .; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H. V.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V. A.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P. D.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision D.01.; Gaussian, Inc.: Wallingford CT, 2013.
(50) Riplinger, C.; Pinski, P.; Becker, U.; Valeev, E. F.; Neese, F. Sparse maps—A systematic infrastructure for reduced-scaling electronic structure methods. II. Linear scaling domain based pair natural orbital coupled cluster theory. *J. Chem. Phys.* **2016**, *144*, 024109.
(51) Dunning, T. H. Gaussian basis sets for use in correlated molecular calculations. I. The atoms boron through neon and hydrogen. *J. Chem. Phys.* **1989**, *90*, 1007−1023.
(52) Grimme, S. Semiempirical hybrid density functional with perturbative second-order correlation. *J. Chem. Phys.* **2006**, *124*, 034108.
(53) Neese, F. The ORCA program system. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2012**, *2*, 73−78.
(54) Neese, F. Software update: The ORCA program system, version 4.0. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2018**, *8*, e1327.
(55) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J. Phys. Chem. B* **2009**, *113*, 6378−6396.
(56) Purvis, G. D.; Bartlett, R. J. A full coupled-cluster singles and doubles model: The inclusion of disconnected triples. *J. Chem. Phys.* **1982**, *76*, 1910−1918.
(57) Legault, C. Y. *CYLview, 1.0b*; Université de Sherbrooke, 2009. (http://www.cylview.org).

https://dx.doi.org/10.1021/acsomega.0c03735
ACS Omega 2020, 5, 26134−26140