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Supporting Information

ABSTRACT: Oxidopyrylium ylides are useful intermediates in synthetic organic chemistry because of their capability of forming structurally complex cycloadducts. They can also self-dimerize via [5 + 3] cycloaddition, which is an oft-reported side reaction that can negatively impact [5 + 2] cycloadduct yields and efficiency. In select instances, these dimers can be synthesized and used as the source of oxidopyrylium ylide, although the generality of this process remains unclear. Thus, how the substitution pattern governs both dimerization and cycloaddition reactions is of fundamental interest to probe factors to regulate them. The following manuscript details our findings that maltol-derived oxidopyrylium ylides (i.e., with ortho methyl substitution relative to oxide) can be trapped prior to dimerization more efficiently than the regioisomeric allomaltol-derived ylide (i.e., with a para methyl substitution relative to oxide). Density functional theory studies provide evidence in support of a sterically (kinetically) controlled mechanism, whereby gauche interactions between appendages of the approaching maltol-derived ylides are privileged by higher barriers for dimerization and thus are readily intercepted by dipolarophiles via [5 + 2] cycloadditions.

INTRODUCTION

[5 + 2] Cycloaddition reactions between oxidopyrylium ylide intermediates and dipolarophiles generate bicyclic compounds of synthetic use (i.e., 1 → 3, Scheme 1), including highly functionalized natural products.† Oxidopyrylium ylide intermediates also have the capacity to dimerize through a [5 + 3] cycloaddition in their neutral form (i.e., 1 → 4, Scheme 1), which is an important process that is in need of more study. A mechanistic understanding of factors that influence oxidopyrylium ylide dimerization is potentially of high value due to the difficulty in controlling the otherwise reactive state of the neutral form.

Our lab has previously focused on intermolecular [5 + 2] cycloaddition reactions with oxidopyrylium ylides generated via deprotonation of kojic acid (5)-derived methyl triflate salts (Scheme 2), first described by Wender.© During the course of these studies, it was revealed that dimer 8 generally forms instantaneously upon the treatment of base, even in the presence of reactive dipolarophiles, but over time, can convert into cycloadducts (i.e., 10).© While it has been proposed that the conversion of the oxidopyrylium dimer to cycloaddition products proceeds by way of cycloreversion back to oxidopyrylium ylides (i.e., 7(−)),© a confounding problem in the validation of this mechanistic hypothesis has been the inability to directly detect the ylides due to their highly reactive
nature. The purification of oxidopyrylium dimer furthermore provides a source of oxidopyrylium ylide free of the Brønsted acid and base and has been advantageous in reaction optimization and total synthesis efforts. However, it should be noted that high temperatures and/or prolonged reaction times are needed, which can present a potential limitation. Thus, understanding how specific structural features influence relative rates of oxidopyrylium ylide dimerization and cycloaddition reactions is of fundamental importance.

Herein, we present experimental and theoretical results on factors that control the dimerization versus cycloaddition behavior of regioisomeric maltol- and allomaltol-derived oxidopyrylium ylides. Specifically, we demonstrate that (i) maltol-derived oxidopyrylium ylide (see 12−c in Scheme 3) is more rapidly trapped by dipolarophiles, such as dimethyl acetylenedicarboxylate (DMAD, 16a), than the allomaltol-derived ylide (7c−); (ii) density functional theory (DFT) calculations show that homodimerization of maltol-derived oxidopyrylium ylide (12−c → 13/14, Scheme 3) proceeds through a concerted process, whereas homodimerization of allomaltol-derived oxidopyrylium ylide (7c− → 8) proceeds through a two-step process that is lower in energy; (iii) kinetic studies for the reaction between homodimers (8/13/14) and DMAD (16a) to form [5 + 2] cycloaddition products reveal different kinetic profiles for the reaction with 8 and that with 13/14, but are each consistent with a mechanism involving full cycloreversion to the oxidopyrylium ylide; and (iv) studies with dipolarophiles are presented to gauge the [5 + 2] cycloaddition trapping efficiencies of the ylides prior to [5 + 3] dimerization.

**RESULTS AND DISCUSSION**

Initial Observations Illustrating Dramatic Reactivity Differences between Maltol- and Allomaltol-Derived Oxidopyrylium Ylides. Our studies began with an evaluation of maltol-derived oxidopyrylium ylides (12−c, Scheme 3A), which were absent from the literature with the exception of a single report by Li.8 Upon synthesizing the maltol-derived oxidopyrylium salt 12 and treating it to triethylamine, we found that two dimers formed in an approximately 2:1 ratio (12 → 13 + 14, Scheme 3A). This result differed from the analogous dimerization of allomaltol-derived salt 7, which led exclusively to a single isomer, 8 (Scheme 3B). Both dimers 13 and 14 reacted with DMAD (16a) at higher temperatures, affording oxidopyrylium cycloaddition product 15a, confirming that these regioisomeric dimers could be used as a ylide source. However, the reactions were noticeably more sluggish than was expected based on our experience with the analogous reaction with dimer 8. In fact, the reaction between either dimer 13 or 14 with DMAD (16a) only reached ~70% conversion after 8 h at 100 °C as compared to that of full conversion within 5 min with dimer 8 in closely related studies (Scheme 3B).4 Consistent with these findings, a competition experiment in which a 1:1 mixture of 8 and 13/14 heated in the presence of 16a and monitored over time led first to the formation 15b, followed by the formation of 15a. Therefore, to promote a higher-yielding process for the cycloaddition with 13/14 and 16a, the reaction was carried out at elevated temperatures (150 °C), which provided 15a in a 95% yield after only 2 h (Scheme 3A).

The more sluggish reactivity between dimers 13 and 14 with DMAD (16a) was surprising to us, especially in light of findings by Li that a closely analogous reaction between 12 and the presumably less reactive indole was completed within 7 h at room temperature.8 Upon closer examination, when a CD3CN solution containing a mixture of oxidopyrylium salt 12 and DMAD (16a) was subsequently treated with N,N-diisopropylamine, after only 30 min at room temperature, 15a was the major product, and dimers 13 and 14 were only
observed as minor products (12 → 15a, Scheme 3A), more closely consistent with the Li studies. The result, however, was highly contradictory to our experience with regioisomeric salt 7, where dimer 8 is almost always observed as the major product upon the addition of base in the presence of dipolarophiles, and over time or at elevated temperature, it converts to cycloaddition products (7 → 8 → 15b, Scheme 3B). Likewise, competition experiments in which a 1:1 mixture of 7 and 12 in the presence of 16a is treated to N,N-diisopropylaniline and monitored over time via 1H NMR resulted in only the appearance of dimer 8 (from 7) and DMAD cycloadduct 15a (from 12).

Given these findings, the dimerization processes were evaluated in the absence of DMAD (16a). Consistent with prior experiences,9 the treatment of salt 7 to N,N-diisopropylaniline led to complete conversion to dimer 8 within 5 min. On the other hand, when salt 12 was treated to identical conditions, conversion to 13 and 14 took upwards of 7 h, and when monitoring the reaction by 1H NMR, no signals were ever observed that could be attributed to ylide 12c−. We initially hypothesized that these slower conversion rates were the result of slower deprotonation, possibly due to an increase in sterics due to the close proximity of the proton to the methyl group of 12. However, the steric hypothesis was disproven since switching to the less sterically demanding base, N,N-dimethylaniline, slowed the consumption of 12 even more so, consistent with the lower pKₐ of N,N-dimethylaniline.9 Likewise, N,N-dimethylaniline slowed down the conversion of salt 7 to dimer 8 to a rate more comparable with the rate that N,N-diisopropylaniline promotes the conversion of 12 to 13 and 14 (Scheme 4A). We thus treated a solution of 7 and DMAD (16a) in CD₃CN to N,N-dimethylaniline to assess whether greater trapping efficiency could be achieved with slower deprotonation. However, when viewed at only a partial conversion of salt 7 (15 min), dimer 8 remained the major product (Scheme 4B).

The above experimental results made it evident that the differences in DMAD (16a) trapping efficiency from salts 7 and 12 prior to dimerization could not be fully explained by simple differences in rates of deprotonation, and thus these differences might exist after the deprotonation step and involve relative reactivities of the ylides. Thus, we turned to DFT calculations to study the relative dimerization and cycloaddition reactions from 7c− and 12c−.

**DFT Calculations.** B3LYP/6-31G(d,p) calculations were employed here. Similar DFT calculations have been used to assess the tendency for compounds to dimerize10 and in cycloadditions of oxidopyrylium ylides.11 To explore the bimolecular pathways (Scheme 5), we have located structures on the potential energy surface (PES) for the dimerization of maltol 12c− and allomaltol 7c− oxidopyrylium ylides. Our calculations focused on the neutral forms of maltol and allomaltol oxidopyrylium ylides since these are expected to give rise to the dimers. Since 7c− and 12c− are structural isomers, their relative energies can be readily compared. The global minimum is the complex of 12c−.

**Scheme 5A** shows the formation of dimer 8 from the allomaltol-derived oxidopyrylium ylide 7c−, which proceeds through a stepwise process. This process involves an initial carbon–carbon bond formation via an aldol-like process between the α-carbon of the embedded enolate of one ylide and the more sterically unencumbered electrophilic carbon of the other. The reaction ΔHf is 8.3 kcal/mol (compared to 7c−) and leads to the second step, where a more sterically encumbered carbon creates the second carbon–carbon bond of dimer 8. In the formation of dimer 8, there is a methyl–methoxy gauche interaction, but it is lower in energy, likely due to the fact that it is an intermolecular process (TS-2, Figure 1). The formation of dimer 13 from maltol oxidopyrylium ylide 12c−, on the other hand, proceeds through an asynchronous concerted process (Scheme 5B). The dimerization of 12c− is higher in energy than the dimerization of 7c− due to an unfavorable methyl–methoxy gauche interaction, producing a ~2 kcal/mol higher transition-state energy (i.e., ΔHf of 11.6 kcal/mol) than that of 7c− (TS-3, Figure 1). An identical ΔHf of 11.6 kcal/mol energy barrier exists in the transition state to dimer 14. Even though sterics of a methoxy group are generally lower in energy than those of a methyl group, this specific methoxy–methyl gauche interaction appears to have added steric strain, where the methyl group of the methoxy extends over the incipient carbonyl group (TS-4, Figure 1). This explains why both dimers of 12c− are formed, in contrast to the selective [5 + 3] dimerization of 7c−.

The cycloaddition reactions between DMAD (16a) and either 7c− or 12c− were fairly analogous energetically, and each was predicted to proceed through a concerted, asynchronous pathway. The transition state between DMAD and 12c− was only slightly favored over that between DMAD and 7c− (11.7 vs 12.9 kcal/mol, Scheme 1S; see the Supporting Information (SI) section for details). Furthermore, cycloaddition products were thermodynamically favored over dimer products by approximately 40 kcal/mol in both cases, consistent with the observations that, with enough time and energy, all of the dimers investigated can be converted to their respective oxidopyrylium [5 + 2] cycloaddition products.

**Kinetic Studies.** Kinetic experiments were carried out as a means to evaluate the relative transition-state energy barriers for dimerization and cycloaddition processes. Drawing inspiration and precedence from classic kinetic studies on the reaction between dialkylborane dimers and alkenes by Brown et al.,12 steady-state approximation was employed to evaluate the reaction between oxidopyrylium dimers (8/13/14) and DMAD (16a) (8 + 16a → 15b or 13/14 + 16a → 15a, Scheme 6). In this way, the kinetics are fixed on the key reactions of interest, namely, the [5 + 2] cycloaddition (k₆).
and dimerization/cycloreversion \( \left( \frac{k_3}{k_{-3}} \right) \) (Scheme 6). Assuming that the energy barrier for the dimerization of \( 12^{(-)} \) is higher than the energy barrier for the cycloaddition reaction with DMAD (16a) to an extent such that \( \frac{1}{2} k_2[16a] \gg k_3[12^{(-)}] \), the reaction should exhibit first-order kinetics, as represented by the equation \(-d[13]/dt = k_3[13]\). Conversely, if the cycloaddition step between \( 7^{(-)} \) and DMAD (16a) is higher in energy than the dimerization of \( 7^{(-)} \) such that \( \frac{1}{2} k_2[16a] \ll k_3[7^{(-)}] \), then the reaction should exhibit three-halves-order kinetics, as represented by the equation \(-d[8]/dt = k_{3/2}[8]^{1/2}[16a]\).

To evaluate the kinetics experimentally, the conversion of 8 and 13 was monitored over time with an excess of DMAD (16a), and the resultant plots were evaluated for best fit (Figure 2A). Consistent with the anticipated kinetics, the conversion of 8 fits best to half-order kinetics \((\ln[8]/t)\) vs time), whereas the conversion of 13 fits best to first-order kinetics \((\ln[13]/t)\) vs time). We also carried out experiments in the inverse, with an excess of the dimers (Figure 2B). In the
presence of dimer 13, the rate of conversion of DMAD (16a) stayed consistent as the concentrations decreased, in line with zero-order kinetics. However, in the presence of dimer 8, the rate changed as the concentration of DMAD (16a) changed, fitting best to first-order kinetics \((\ln[16a])_{\text{vs}} \text{time}\). Experiments performed with 14 were also consistent with those performed with 13 (see the Supporting Information). Thus, these studies provided experimental evidence that in the reaction between allomaltol-derived oxidopyrylium ylides 7(−) and 16a, dimer 8 is the kinetic product, helping explain the difficulty of intercepting 7(−) with DMAD (16a). Conversely, the studies also provided experimental evidence that in the reaction between maltol-derived oxidopyrylium ylides 12(−) and 16a, cycloaddition product 15a is the kinetic product, which explains why 12(−) can be successfully intercepted with DMAD (16a).

**Dipolarophile Dependence.** Both DFT calculations and kinetic experiments helped explain why DMAD (16a) is trapped more efficiently by 12(−) than by 7(−). We next wanted to gauge how their relative trapping efficiency might extend to other dipolarophiles. For these studies, we added \(N,N\)-diisopropylaniline to a solution of CD$_3$CN containing oxidopyrylium salts 7 and 12 and a panel of dipolarophiles of varying reactivities (16a−d) and monitored the reaction progress by \(^1\text{H} \text{NMR (Scheme 7)}\). Phenylacetylene (16d) is known to react more sluggishly with 7(−) than DMAD (16a).\(^7\) Transition-state energy barriers were thus computed for the reaction of 16d with 7(−) to form 15g (\(\Delta H^\ddagger = 16.3 \text{ kcal/mol, Scheme 25}\); see the SI section for details) and for the reaction of 16d with 12(−) to form 15h (\(\Delta H^\ddagger = 17.4 \text{ kcal/mol, Scheme 25}\); see the SI section for details). As these energy barriers are each higher than their respective dimerization energy barriers, dimerization products should be the kinetic products in both instances. Consistent with this hypothesis, when \(N,N\)-diisopropylaniline was treated to a mixture of 16d and either salt 7 or 12, upon complete consumption of salts, only dimerization products were observed (see the entry for products 15g/h).

For a more reactive dipolarophile, we turned to the highly electrophilic 4-phenyl-1,2,4-triazole-3,5-dione (PTAD, 16b; see the entry for products 15c/d).\(^4\) As anticipated, very low transition-state energy barriers were calculated for the reaction between 16b and both 7(−) (\(\Delta H^\ddagger = 2.7 \text{ kcal/mol}\) and 12(−) (\(\Delta H^\ddagger = 3.1 \text{ kcal/mol, Scheme 35}\); see details in the SI section). As these barriers were each substantially lower than those of their respective dimerization reactions, both 15c and 15d would be expected to be the kinetic products. Consistent with this, when \(N,N\)-diisopropylaniline was treated to a mixture of 16b and either salt 7 or 12, no dimer was observed and the [5 + 2] cycloaddition products 15c and 15d predominated. These two sets of experiments demonstrated that with the more extremes on the dipolarophile reactivity spectra, the trapping efficiencies of the two salts are similar. However, when these experiments were performed with the more intermediately reactive dipolarophile, methyl propiolate (16c; see the entry for products 15e/f), differences in the trapping efficiencies of 7(−) and 12(−) returned. Specifically, when salt 7 was treated to the base in the presence of 16c, only dimer 8 was observed, whereas significant amounts of product 15e were observed in the analogous reaction with 12.

**Mechanistic Interpretation and Implications.** Oxidopyrylium ylides 7(−) and 12(−) can undergo both [5 + 3] dimerization and [5 + 2] cycloaddition chemistry to generate dimers (8, 13, 14) or cycloaddition products (i.e., 15a/b), respectively. The dimerization to 8 and 13/14 is reversible and leads back to the ylides, which can then convert further to the thermodynamically stable oxidopyrylium cycloaddition products, 15a and 15b, when heated in the presence of DMAD (16a). Instead of the dimer reacting directly with the dipolarophile, the kinetic and computational results support a mechanism, whereby dimer conversion to cycloaddition products proceeds through the cycloreversion of the dimers to oxidopyrylium ylides followed by a cycloaddition reaction. Kinetics for these two reactions is different, however. Kinetics from the reaction from dimer 8 and DMAD (16a) is consistent with a mechanism wherein the transition-state energy for [5 + 3] cycloreversion/dimerization is lower than that of the [5 + 2] cycloaddition reaction, and that from 13/14 consistent with one where the transition state for [5 + 3] cycloreversion/dimerization is higher in energy than that for the [5 + 2] cycloaddition step.

DFT studies were consistent with these trends, revealing that the transition-state barrier for the dimerization of 12(−) is higher in energy than that of 7(−) (Scheme 5), and thus 8 is the kinetic product relative to 15a, whereas 15b is the kinetic product relative to 13/14. The DFT studies indicate that these energy differences are the result of unavoidable steric interactions in the transition state toward both dimers 13 and 14, which alter the mechanism for the different dimerization reactions. The implications to these studies are that by positioning groups ortho to the oxide (e.g., 12(−)), the transition-state barrier toward dimerization can increase and improve the success rate of trapping the ylide with a dipolarophile prior to self-dimerization. One could anticipate based upon these results that by increasing the size of these groups, the rate of dimerization will be slowed even further and
allow for an even more efficient \([5 + 2]\) trapping. Indeed, 2,4,6-tri phenylpyrylium-3-oxide is one of the few oxidopyrylium ylides to ever be observed experimentally and does not dimerize,\(^7\) which may be why it reacts with an extremely broad range of dipolarophiles.\(^8\) In the current studies, dramatic differences in trapping efficiency were observed with DMAD (16a) and methyl propiolate (16c). However, the more reactive dipolarophile PTAD (16b) efficiently intercepted both ylides, whereas the less reactive dipolarophile phenylacetylene (16d) could not intercept either ylide. Thus, further structure–activity relationships with a broader range of both oxidopyrylium ylides and dipolarophiles are warranted.

## CONCLUSIONS

Synthetic, kinetic, and theoretical approaches have been developed to probe oxidopyrylium ylide reactivity in self-dimerization and cycloaddition reactions. We find the following results: (i) maltol- and allomaltol-derived oxidopyrylium salts serve as precursors to their corresponding oxidopyrylium ylides \(7^-\) and \(12^-\), which themselves serve as intermediates in both self-dimerization and cycloaddition reactions; (ii) DFT calculations provide valuable insight into the dimerization mechanism of these two oxidopyrylium ylides where gauche methyl/methyl or methyl/methoxy interactions favor the dimerization in a kinetically not thermodynamically controlled fashion compared to the \([5 + 2]\) cycloaddition selectivity; (iii) kinetics for the reaction between dimethyl acetylenedicarboxylate (DMAD) and oxidopyrylium ylides suggests that the rate-limiting step with dimer 8 is the cycloaddition reaction; in contrast, the reaction with dimer 13 or 14 is consistent with a mechanism where the rate-limiting step is the cycloreversion to ylide \(12^-\); (iv) while oxidopyrylium ylides \(7^-\) and \(12^-\) have very different trapping efficiency profiles with DMAD (16a) and methyl propiolate (16c), only cycloaddition products form in the presence of the more reactive dipolarophile (16b), and only dimers form in the presence of the less reactive phenylacetylene (16d). These studies provide insight into how differences in the structure of the oxidopyrylium ylides such as the placement of appendages can lead to significantly different reactivity behaviors. Future studies combining synthetic, kinetic, and theoretical studies across a broader range of oxidopyrylium ylides should further enhance our understanding of these systems and help inform future synthetic strategies employing oxidopyrylium cycloaddition and dimerization reactions. For example, the decomposition of homodimers is a retro reaction of “masked” neutral oxidopyrylium ylide monomers and is a base-free strategy that could be valuable for some reactions. In contrast to the reactivity of DMAD with dimers 8, 13, and 14, Hendrickson’s early work described how the reaction between the dimer of an unsubstituted 3-oxidopyrylium ylide and DMAD only forms trace products, even at 200 °C.\(^{20}\) Thus, there appear to be structural advantages to dimers 8, 13, and 14 that allow them to behave as oxidopyrylium ylide sources. It appears reasonable to hypothesize that the OMe plays an important role in this reactivity by both enhancing the nucleophilicity of the ylides and destabilizing the ground state of 8 and 14 through the gauche interactions it presents. Further studies are underway to assess the importance of the OMe group for efficient dimerization reversibility and whether other oxidopyrylium ylide dimers without OMe groups may also behave as ylide sources. In other instances, dimerization may pose greater technical challenges, and knowledge of how to effectively trap out ylides prior to dimerization will be valuable.

## EXPERIMENTAL SECTION

**General Information.** All starting materials and reagents were purchased from commercially available sources and used without further purification, with the exception of CH$_3$Cl$_2$, which was purified on a solvent purification system prior to reactions. \(^1H\) and \(^13C\) NMR shifts were measured using the solvent residual peak as the internal standard and reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, q = quartet, m = multiplet), coupling constant (Hz), integration. Infrared (IR) spectral bands are characterized as strong (br), strong (s), medium (m), and weak (w). Mass spectra were recorded on a spectrometer by the electrospRAY ionization (ESI) technique with a time-of-flight (TOF) mass analyzer. Microwave reactions were performed via the Biotage Initiator EXP US (manufacturer #: 355302) (external IR temperature sensor) in a sealed vessel. Where noted, reaction products were purified via silica gel chromatography using a Biotage Isolera Prime, with Biotage SNAP Ultra 10 g or 25 g cartridges, in a solvent system of ethyl acetate (EtOAc) in hexane.

**Synthesis and Characterization of Maltol-Derived Oxido- pyrylium Salt.** 3-Hydroxy-4-methoxy-2-methylpyrylium Trifluoromethanesulfonate (12). To a solution of maltol (11, 5 g, 0.0396 mol) in CH$_3$Cl$_2$ (10 mL) was added methyl trifluoromethanesulfonate (MeOTf, 6.5 mL, 0.0594 mol). The reaction was allowed to stir at reflux for 4 h, cooled to an ambient temperature, and then evaporated under reduced pressure to yield 12 as white crystals (6.5 g, 54% yield), with a melting point range of 99–102 °C. IR (thin film, KBr): 3088 (w), 1634 (s), 1554 (w), 1497 (m), 1438 (w), 1258 (b), 1164 (s), 1069 (w), 1033 (s), 962 (w), 903 (w), 827 (w), 750 (b), 636 (s) cm$^{-1}$. \(^1H\) NMR (400 MHz, CD$_3$CN) $\delta$ 8.80 (d, $J = 5.2$ Hz, 1H), 7.60 (d, $J = 5.2$ Hz, 1H), 4.31 (s, 3H), 2.68 (s, 3H). \(^13C\)(\(^1H\)) NMR (101 MHz, CD$_3$CN) $\delta$ 168.8, 166.4, 161.2, 142.9, 108.5, 60.7, 16.3.  

**Synthesis and Characterization of Maltol-Derived Oxidopyrylium Dimers (13) and (14).** In a round-bottom flask, tritile salt 12 (0.1 g, 0.345 mmol, 1 equiv) was suspended in CH$_2$Cl$_2$ (3 mL, 0.1 M). Triethylamine (96 µL, 0.690 mmol, 2 equiv) was slowly added to the reaction mixture, at which time the solid slowly dissolved. The reaction mixture was allowed to stir for 2 h at room temperature and then quenched with saturated aqueous ammonium chloride (5 mL). The organic layer was isolated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organics were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude material was purified by chromatography (Biotage Isolera Prime, SNAP 12 g silica gel, 18 cm × 1.8 cm solvent gradient: 0–25% EtOAc in hexanes (500 mL)). Two products were separated, and product fractions were concentrated to yield 13 (22 mg, 0.0786, 45% yield) and 14 (12 mg, 0.0429, 25% yield), both isolated as white solids.  

\[±-(1R,2R,6S,7R)-6,9-Dimethoxy-1,2-dimethyl-3,11-dioxatricyclo[5.3.1.1\(2,6\)]dodeca-4,9-diene-8,12-dione (13).\] Mp: 129–132 °C. \(R_f\) = 0.14 in 20% ethyl acetate in hexanes: IR (ATR, ZnSe) 3090 (w), 3002 (w), 2941 (br), 2834 (br), 1742 (s), 1699 (s), 1626 (s), 1590 (s), 1467 (s), 1358 (m), 1258 (m), 1170 (s), 1139 (s), 1066 (s), 1036 (m), 914 (m), 841 (w), 789 (w). \(^1H\) NMR (400 MHz, CD$_3$CN) $\delta$ 6.67 (d, $J = 5.9$ Hz, 1H), 6.01 (d, $J = 5.1$ Hz, 1H), 5.02 (d, $J = 5.9$ Hz, 1H), 4.49 (d, $J = 5.1$ Hz, 1H), 3.63 (s, 3H), 3.49 (s, 3H), 1.55 (s, 3H), 1.25 (s, 3H). \(^13C\)(\(^1H\)) NMR (101 MHz, CD$_3$CN) $\delta$ 199.5, 188.8, 149.9, 148.2, 113.0, 100.5, 92.4, 87.6, 86.3, 77.4, 55.5, 54.1, 17.3, 14.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ calc for C$_{10}$H$_{14}$O$_5$: 201.0473. Found: 201.0476.

\[±-(1R,2R,6R,7R)-6,9-Dimethoxy-2,7-dimethyl-3,11-dioxatricyclo[5.3.1.1\(2,6\)]dodeca-4,9-diene-8,12-dione (14).\] Mp: 159–159 °C. \(R_f\) = 0.14 in 25% ethyl acetate. IR (ATR, ZnSe) 3090 (w), 3002 (w), 2941 (br), 2834 (br), 1742 (s), 1699 (s), 1626 (s), 1545 (w), 1358 (m), 1258 (m), 1170 (s), 1139 (s), 1066 (s), 1036 (m), 914 (m), 841 (w), 789 (w). \(^1H\) NMR (400 MHz, CD$_3$CN) $\delta$ 6.69.
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Rf vacuo to yield EtOAc in hexanes (500 mL)). Product fractions were concentrated in vacuo to yield a mixture of dimer (s, 3H). 13C{1H} NMR (101 MHz, CDCl3)

Supporting information for this article, including synthesis details, can be found in the supplementary material.

Synthesis of New Oxidopyrylium [5 + 2] Cycloadducts for Characterization. Cycloadducts 15b, 15f, and 15h were synthesized as follows to provide characterization data in support of 1H NMR yields described in Scheme 7.

(±)-Dimethyl (15S,5S)-3-Methoxy-5-methyl-4-oxo-8-oxabicyclo[3,2.1]octa-2,6-diene-6,7-dicarboxylate (25). To a solution of 13/14 (20 mg, 0.0714 mmol, 1 equiv) in CDCl3 (1 mL, 0.9 M) was added dimethyl acetylenedicarboxylate (60 mg, 0.344 mmol, 2 equiv) in CD3CN (600 μL, 0.2068 mmol, 1.2 equiv). The reaction was stirred for 5 min and then immediately purified by chromatography (Biotage Isolera Prime, SiliCycle SiliaSep 25 g silica gel column, 40−63 μm 60 Å, solvent gradient: 0−100% EtOAc in hexanes (500 mL)). Product fractions were concentrated in vacuo to yield 15a as a white solid (39 mg, 72% yield). Mp: 65 °C.

Separately. To dimer (15a, 15b, 15c, 15d, 15e, and 15g) were synthesized as follows to provide characterization data in support of 1H NMR yields described in Scheme 7.

Computational Methods. Optimizations, frequency calculations, and the intrinsic reaction coordinate calculations were performed with Gaussian 09 (revision D.01)17 at the B3LYP/6-31G(d,p) level of theory18 and visualized with Gaussview 5.0.19 These calculations established the nature of the stationary point obtained. Vibrational potential energy surface (PES) in Scheme 5, frequency calculations informative for the potential energy surface (PES) in Scheme 5, frequency calculations were used to calculate the relative energies of the products. Vibrational analyses showed that TS−1−TS−4 species were transition structures, while 2−5. DOI: 10.1021/acs.joc.9b02137 J. Org. Chem. 2019, 84, 14670−14678

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The structures of 8, 13, and 14 are the first to be determined for these tricyclic heterocycles, and they confirm the proposed structures. Crystals were grown using the vapor diffusion technique, using minimal ethyl acetate to solubilize dimers and hexanes as the outer solvent. The crystals of 13 and 14 appeared to be split crystals, most likely with more than two domains, giving rise to relatively high residuals due to overlapping peaks, and in addition, 13 was not strongly diffracting. The X-ray intensity data were measured on a Bruker Smart Breeze CCD system equipped with a graphite monochromator at 100(2) K and cooled by an Oxford Cryosystems Cryostream. A total of 1464 frames were collected and integrated with the Bruker SAINT software package, using a narrow-frame algorithm. Data were corrected for absorption effects using the multiscan method (SADABS or TWINABS). The structures were solved and refined using the Bruker SHELXTL software package. All data and methods may be found in the cif files included in the Supporting Information. Briefly, the refinement of 8 was routine, and 13 was refined as a two-component twin. Compound 14 had to be refined as a two-component twin but the second domain refined to just 2% and also exhibited a ~1:1 disorder for molecule 2 of the two in the asymmetric unit, for one methoxy methyl and one methyl group.

Cambridge Crystallographic Data Centre deposition numbers for 8, 13, and 14: CCDC 1935838, 1935839, and 1935840.

■ ASSOCIATED CONTENT

S Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b02137.

Crystallographic data for compound 8 (CIF)
Crystallographic data for compound 13 (CIF)
Crystallographic data for compound 14 (CIF)

1H and 13C NMR spectra of all new compounds, a discussion on the characterization of 15d as a mixture, including 1H and 13C NMR data of PTAD (16d) and dimer 8, graphs used to determine kinetic rate data, DFT computed data, and X-ray data for 8, 13, and 14 (PDF)

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Notes
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■ ADDITIONAL NOTE

For compound 15d, aromatic regions are undefined due to the presence of PTAD overlapping in the aromatic region. See supporting information for further details.

■ REFERENCES


