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Strained to the Limit: When a Cyclobutyl Moiety Becomes a Thermodynamic Sink in a Protolytic Ring-Opening of Photogenerated Oxetanes

Roman A. Valiulin, Teresa M. Arisco, and Andrei G. Kutateladze*

Department of Chemistry and Biochemistry, University of Denver, Denver, Colorado 80208

akutatel@du.edu

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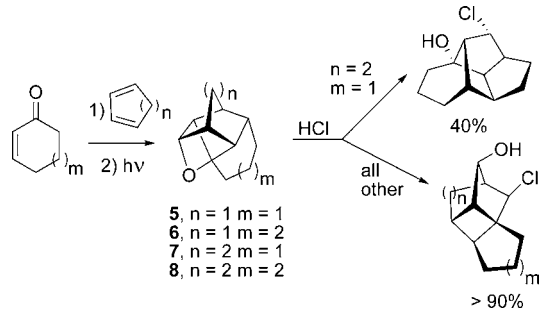
ABSTRACT

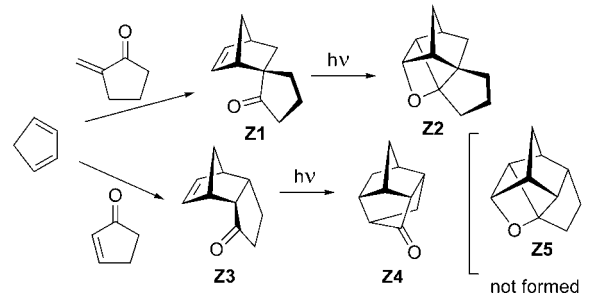


Strained polycyclic oxetanes generated photochemically from the Diels−Alder adducts of cyclic dienes and enones undergo deep skeletal rearrangements under protolytic ring-opening conditions offering expeditious access to chlorohydrins and other products of unique skeletal topology.

As popularized by Sauers,[1] acyl norbornenes undergo an intramolecular Paternò-Büchi (*P.-B.*) reaction yielding reactive oxetanes which can be further modified by ring-opening either via acid-catalyzed reactions or reduction. This harvesting of the strain installed by a photochemical step to access targets otherwise not easily accessible via the ground state chemistry has been used in a number of examples, including Rawal's reductive fragmentation providing access to diverse di- and triquinanes,[2] photo-induced oxametathesis,[3,4] etc.

Sauers also examined the photochemistry of "polycyclic acylnorbornenes," poised to further increase the strain. For example, the spiro-connected ketone **Z1** gave the *P.-B.* product **Z2**. However, the "fused" cyclopentenone adduct **Z3** did not produce the expected oxetane **Z5**, but rather gave a product **Z4** rationalized in terms of the $\pi-\pi^*$ excited state of the alkene moiety (Scheme 1).[1e]

Scheme 1[a]



[a] From ref 1e.

(1) (a) Sauers, R. R.; Kelly, K. W. *J. Org. Chem.* **1970**, *35*, 498–501. (b) Sauers, R. R.; Whittle, J. A. *J. Org. Chem.* **1969**, *34*, 3579–3582. (c) Sauers, R. R.; Schinski, W.; Mason, M. M. *Tetrahedron Lett.* **1969**, 79–82. (d) Sauers, R. R.; Kelly, K. W.; Sickles, B. R. *J. Org. Chem.* **1972**, *37*, 537–543. (e) Sauers, R. R. *J. Org. Chem.* **1974**, *39*, 1850–1853.

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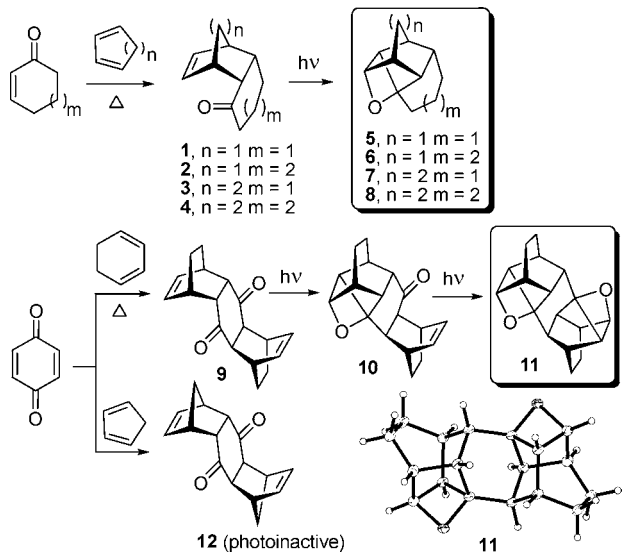
This failure to form **Z5** has probably discouraged subsequent *P.-B.* studies of fused polycycles, as there is only a partially relevant 1977 Paddon-Row's account[5a] found in the literature—later confirmed by Coxon[5b]—where a *P.-B.* channel competes with an all-carbon $[2_\pi+2_\pi]$ photocyclization in a hemicyclone-benzoquinone adduct.

We hypothesized that a modest increase in the ring size of either the dienophile or diene could relieve the strain and restore the Paternò-Büchi photoreactivity in fused polycyclic systems of type **Z3**. Our Density Functional Theory (DFT) calculations at the B3LYP/6-311+G(d,p) level confirmed that oxetane **Z5** relaxes by as much as 11 kcal/mol when its cyclopentyl moiety is expanded by a single methylene group, suggesting that the Diels−Alder (*D.-A.*) adducts of *six*-membered and larger cycloalkenones can be *P.-B.* photoreactive.

We now report that the *D.-A.* adducts of 2-cyclohexenone and 2-cycloheptenone[6] are indeed capable of forming strained polycyclic oxetanes upon irradiation (Scheme 2).[7] Strikingly, even the bis-adduct of cyclohexadiene and benzoquinone **9**[8] was found to be photoactive, producing C_2-symmetric dioxetane **11** via the monooxetane **10** when irradiated.

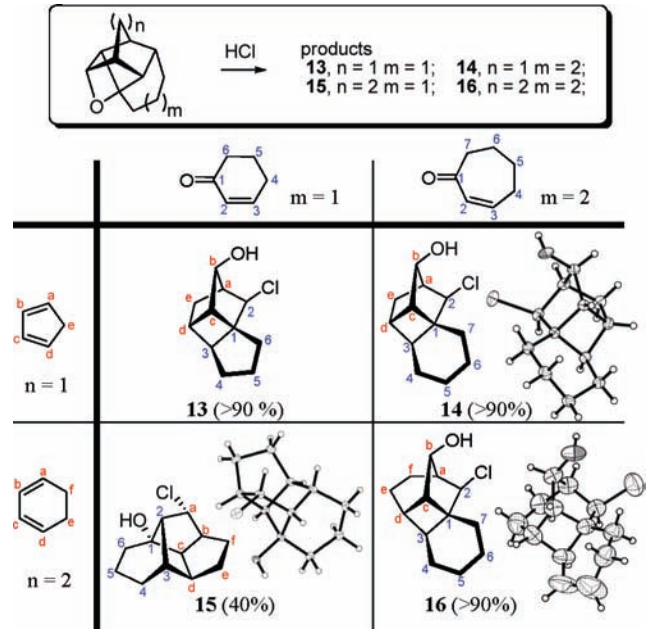
Scheme 2



In the bis-series, the photoreactivity limit is reached with the cyclopentadiene adduct **12**, which does not form even a monooxetane, unlike the similarly sized cyclohexano-norbornene **1**, which is photoactive. This further confirms that flexibility of the ketone-containing ring is critical. Unlike **1**, the six-membered ring in **12** is further constrained by the second rigidly fused norbornyl moiety.

According to our DFT calculations these polycyclic oxetanes are still far more strained than their spiro counterparts (such as **Z2** in Scheme 1). As such, they readily undergo acid-catalyzed ring-opening and subsequent cationic rearrangements, conforming to certain computationally predictable topologies consistent with the structure of the initial polycyclic enone (Scheme 3).

Scheme 3



When treated with HCl, oxetanes usually produce 1,3-chlorohydrins. However, in the case of strained oxetanes **5**−**8** and **11**, which can potentially open to form both tertiary or secondary carbocations, the produced chlorohydrins resulted from more elaborate cationic rearrangements.[9]

Relative stability of the tertiary cation depends on the degree of its pyramidalization, which in these systems is defined primarily by the size of the enone ring. Our rationale is that for larger rings ($m > 1$) the acid-catalyzed oxetane ring-opening preferentially produces the expected tertiary cation of type **A1**, Scheme 4A. While relatively more stable

(2) (a) Rawal, V. H.; Dufour, C. *J. Am. Chem. Soc.* **1994**, *116*, 2613–2614. (b) Dvorak, C. A.; Dufour, C.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1998**, *63*, 5302–5303.

(3) Valiulin, R. A.; Kutateladze, A. G. *Org. Lett.* **2009**, *11*, 3886–3889.

(4) Pérez-Ruiza, R.; Miranda, M. A.; Alleb, R.; Meerholzb, K.; Griesbeck, A. G. *Photochem. Photobiol. Sci.* **2006**, *5*, 51–55.

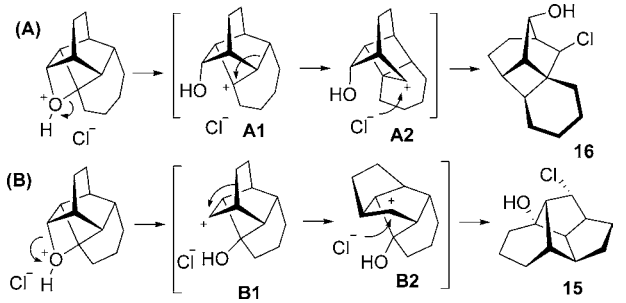
(5) (a) Warrener, R. N.; McCay, I. W; Paddon-Row, M. N. *Aust. J. Chem.* **1977**, *30*, 89–94. (b) Coxon, J. M.; O'Connell, M. J.; Steel, P. J. *Aust. J. Chem.* **1986**, *39*, 1537–1557.

(6) Synthesis of *D.-A.* adducts **1**−**4**, **9**, **12** is described in the literature: (a) Fringuelli, F.; Guo, M.; Minuti, L.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1989**, *54*, 710–712. (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458–2460. (c) Rathore, R.; Kochi, J. *J. Org. Chem.* **1995**, *60*, 4399–4411.

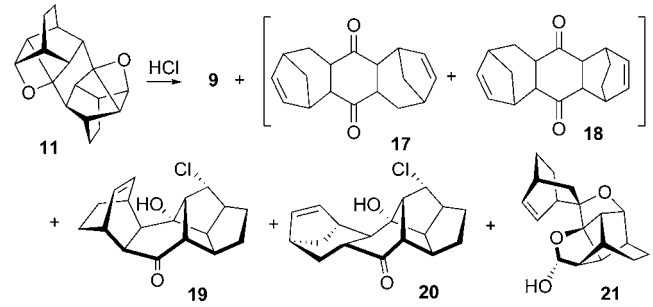
(7) In a typical procedure, 3−10 mM solution of ene-one precursors **1**−**4**, **9** in CH_3CN (or benzene) was irradiated in a quartz tube in the Rayonet reactor equipped with RPR-3000 UV lamps (broadband 250−350 nm UV source with peak emission at 300 nm) for 24−72 h. Conversion was monitored by NMR, the oxetanes were used without further purification. Oxetanes **5**−**8**, **10**−**11** have a very characteristic low field multiplet at 4.0−4.5 ppm, $W_{1/2} \approx 7$ Hz. We also were able to accurately calculate their NMR spectra—see SI. Attempts to further purify reaction mixtures by column chromatography were mainly unsuccessful, as the strained polycyclic oxetanes **5**−**8** are not stable on silica gel, producing varying amounts of rearranged products.

(8) see Rathore, R.; Kochi, J. *J. Org. Chem.* **1995**, *60*, 4399–4411.

Scheme 4



Scheme 5



than the alternative secondary cation, **A1** is still destabilized by forced pyramidalization. It relaxes by (remarkably) rearranging into **A2** possessing a cyclobutyl moiety. **A2** is then trapped by the chloride anion to yield the observed products **13**−**14** and **16**.

We note that the stereochemical outcome of this two step rearrangement is inversion at each step, which implies that the whole sequence might be a concerted reaction or nearly so.

For $m = 1$, that is, the smallest ring size at which Paternò-Büchi cyclization is possible in this series, the tertiary cation is even more destabilized. It is plausible that the two cations are formed reversibly and competitively. The outcome in this case depends on "*n*", that is, the size of the top bridge. With $n = 2$, Scheme 4B, upon formation of a secondary cation **B1**, the two carbon bridge undergoes 1,2-shift to give **B2**, which is trapped by the chloride anion. Again, all steps in the B-sequence occur with inversion of configuration, which hints at a semiconcerted mechanism.

In the case when both $m = 1$ and $n = 1$ as in **5**, the single methylene bridge fails to migrate and pathway A prevails, yielding cyclobutane **13**.

As is clearly demonstrated, protolytic heterolysis of a C−O bond in oxetanes **5**−**8** provides insufficient relief of strain installed at the photochemical step, and therefore subsequent carbocationic rearrangements accompany the oxetane ring-opening.

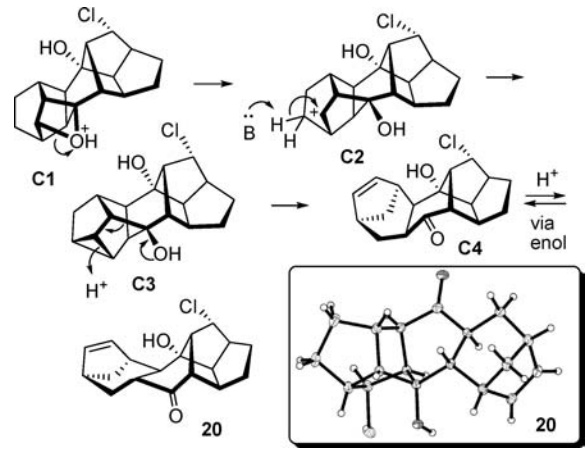
The polycyclic oxetanes are very reactive; they do not generally survive column chromatography. This is especially true for bis-oxetane **11**. We found that unlike oxetanes **5**−**8**, bis-oxetane **11** undergoes a number of competing ring-openings and rearrangements under acid-catalyzed conditions, Scheme 5. The major product is an isomer of the starting diene **9** for which we tentatively assign structure **17**. The rearranged bicyclo[3.2.1] moiety of **17** (and of its minor isomer **18**) is inferred from the NMR data and by analogy with the X-ray structure of chlorohydrin **20** which has this moiety. Structures of chlorohydrin **19** and hemiacetal **21** were also elucidated by X-ray crystallography.

It appears that bis-oxetane **11**, as most extremely strained, offers a variety of deep skeletal rearrangements under protolytic ring-opening conditions. We note, however, that perhaps for this very reason the selectivity and reproducibility of the reaction shown in Scheme 5 was poor. In several runs alkene **17** was forming at 40−50% yield, whereas the yields of products **18**−**21** never exceeded 10%.

Chlorohydrins **19** and **20** are expectedly related to product **15**, which further confirms the generality of the rearrangement shown in Scheme 4B for the oxetanes derived from six membered dienes and dienophiles.

The alkene moiety of **19** probably resulted from an acid-catalyzed cycloreversion in the initial oxetane, whereas chloride **20** has a rearranged olefinic half. A plausible mechanism for this rearrangement yielding the bicyclo[3.2.1] moiety in **20** and, by analogy in **17** and **18**, is shown in Scheme 6. We hypothesize that cyclopropane **C3** is the key intermediate in the formation of **20**. While formation of nortricyclenes is common in solvolytic transformations of bicyclo[2.2.1]heptanes, similar tricyclenes have been reported in the bicyclo[2.2.2]octane series as well.[10]

Scheme 6



According to a force field estimate, the formation of **C3** from its precursor oxetane is about 20 kcal/mol downhill.

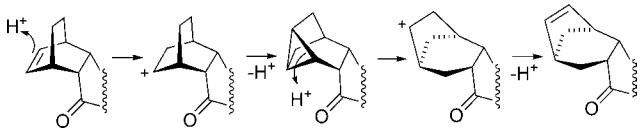
(9) A typical protolytic ring opening procedure: To a 3−10 mM solution of oxetanes **5**−**8**, or **11** in CH_2Cl_2, 1−3 mol equiv of HCl (4.0 *M* solution in dioxane) was added. The resulting mixture was stirred at ambient temperature for 24 h, the solvent was removed in vacuum, and the products were purified by chromatography on a silica gel column using hexane-ethyl acetate (or hexane-ethanol) as eluent .

(10) Alder, R. W.; Carta, F.; Reed, C. A.; Stoyanova, I.; Willis, C. L. *Org. Biomol. Chem.* **2010**, *8*, 1551–1559.

Acid-catalyzed cyclopropyl ring-opening in **C3** followed by Grob fragmentation gives the cis-fused alkene **C4**, which equilibrates via an enol intermediate into **20**. Product **20** has trans-stereochemistry and is 1.5 kcal/mol more stable than **C4**.[11]

We suggest that the rearranged major alkene **17** (and the minor isomer **18**) are formed via a similar mechanism. Since a small amount of the starting diene **9** is always formed by acid-catalyzed cycloreversion, one notes that alternatively the [2.2.2] → [3.2.1] transformation can be achieved by simply protonating the alkenyl moiety in diene **9** as shown in Scheme 7.

Scheme 7



However, this mechanism was ruled out because diene **9**, when treated with HCl under the same reaction conditions, does not yield rearranged diene **17**.

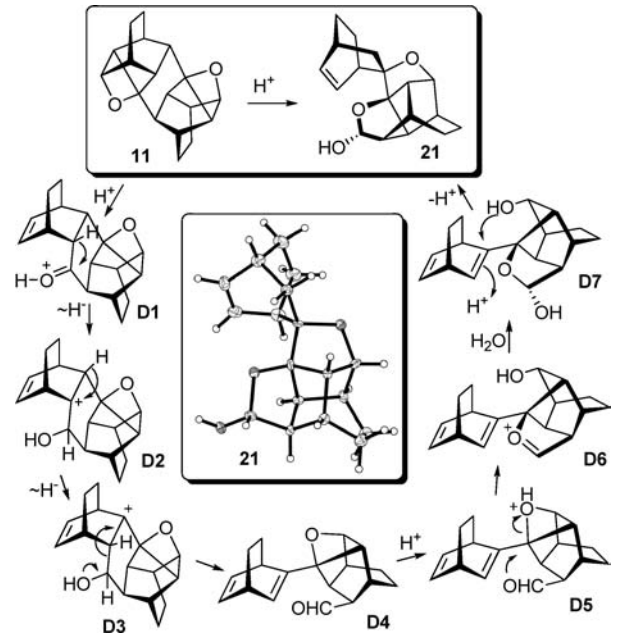
Arguably, the most spectacular transformation in this series produces hemiacetal **21**. Our rationale for its formation is presented in Scheme 8, which starts with the retro *P.-B.* (consistent with the formation of both **19** and **21**).

The critical **D3→D4** Grob-type fragmentation is set up by two consecutive 1,2-hydride shifts, where the first shift, **D1→D2**, amounts to a retro-pinacol rearrangement. Acid-catalyzed oxetane ring-opening in **D4**, accompanied by the capture of the generated carbocation with the formyl group and subsequent conjugate electrophilic addition to the double bond in the bicyclo[2.2.2]octadiene moety of **D7**, furnishes the spiro-product **21**, (its X-ray structure is shown).

In summary, strained polycyclic oxetanes can be synthesized photochemically from the *D.-A.* adducts of cyclic dienes and enones generally as long as the dienophile has a ring size greater than five. Such oxetanes harvest and store

(11) Notice that the same outcome can be achieved with an alternating sequence of (1,3-hydride)-(1,2-alkyl)-(1,3-hydride) shifts.

Scheme 8



excited state energy, which can be utilized to access unique functionalized polycyclic scaffolds via acid-catalyzed oxetane ring-opening and subsequent deep cationic rearrangements. Given that during the past decade *enantioselective catalytic* Diels−Alder reactions of cycloalkenones have been developed, starting with MacMillan's pioneering studies,[6b] the photoprotolytic one-pot transformations described here may offer expeditious access to a variety of enantiopure functionalized polycycles.

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Supporting Information Available: Experimental details, NMR and X-ray characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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