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Direct observation by ^{1}H NMR of 4,5-benzoxepin-2,3-oxide and its surprisingly rapid ring-opening rearrangement to 1*H*-2-benzopyran-1-carboxaldehyde ☆

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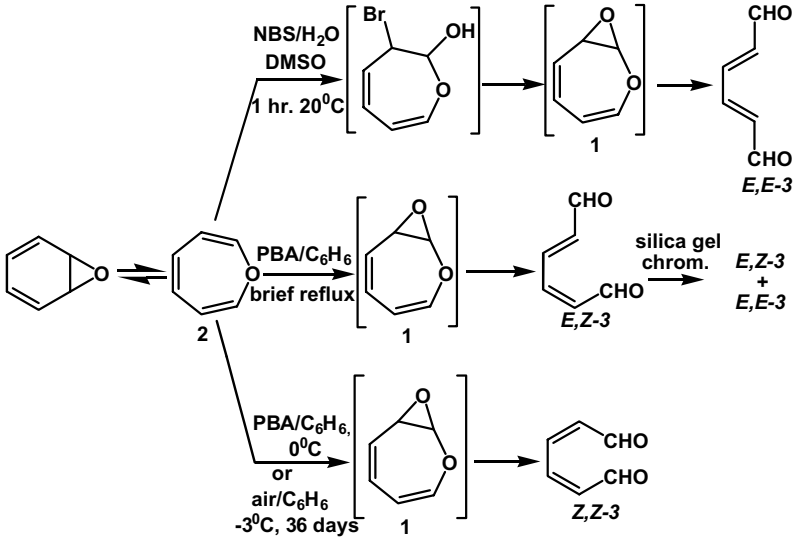
Abstract—The first unambiguous observation of an oxepin-2,3-oxide is reported. Between 5 and 10 °C it rearranges rapidly to its isomer 1*H*-2-benzopyran-1-carboxaldehyde. In contrast, 2,3-oxides of monocyclic oxepins rearrange to stable, ring-opened dialdehydes or diketones.

Oxepin-2,3-oxide (or 2,3-epoxyoxepin,[1] **1**) and its derivatives have, in all likelihood, been generated but have thus far eluded both isolation and unambiguous spectroscopic observation.[1–5] Davies and Whitham[2] explored four different pathways for epoxidation of oxepin (**2**) and isolated only stereoisomers of muconaldehyde (**3**), assumed to be reaction products of the putative epoxide **1** (see Scheme 1). In order to further support **1** as the source of the muconaldehydes, they reacted 2,7-dimethyloxepin (**4**) and indane 3a,7a-oxide



Scheme 1.

Keywords: Oxepins; Dimethyldioxirane; Benzene oxidation.
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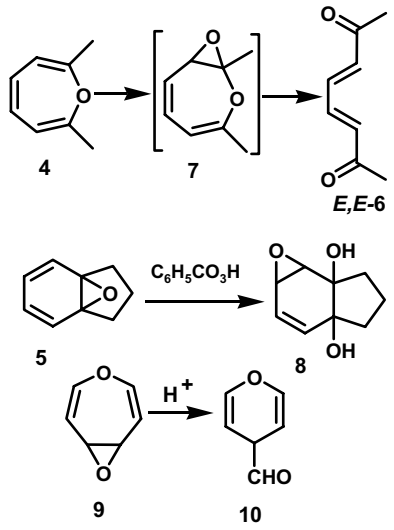


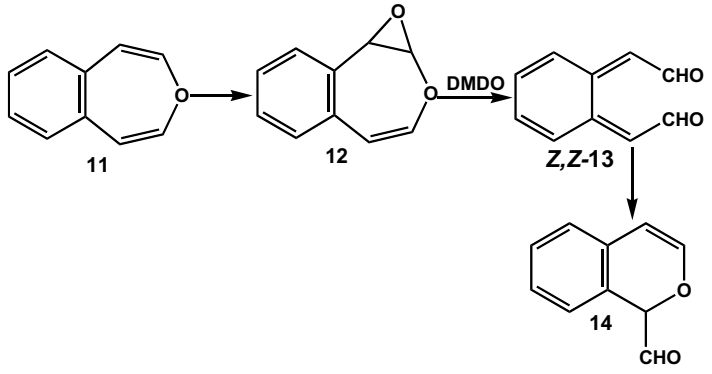
Scheme 2.

(**5**) with perbenzoic acid (PBA) (see Scheme 2). In contrast to the parent compound oxepin, 2,7-dimethyloxepin has no detectable oxide tautomer and its epoxidation yields exclusively the ring opened monooxygenation product **6** (and no detectable **7**).[2] The oxepin tautomer of **5** is highly strained, much less stable than **5**, and thus, oxidation of **5** yields epoxide **8** (Scheme 2). The apparent lability of oxepin-2,3-oxide under the conditions employed by Davies and Whitham might be the result of an intrinsically low energy barrier toward rearrangement (see below) as well as the consequence of the acidity of classical epoxidation reactions with reagents such as PBA. For reference, oxepin-4,5-oxide (**9**) is calculated to be about 4 kcal/mol less stable than its isomer **1**.[6] It has been synthesized in a five-step procedure from **2**, is thermally stable to 120 °C, and rearranges in acidic solution to 4*H*-pyran-4-carboxaldehyde (**10**, see Scheme 2).[7]

Dioxirane reagents, including dimethyldioxirane (DMDO) and methyltrifluoromethyldioxirane (MTDO), are known and found to be effective low-temperature, non-acidic epoxidation reagents[8] that offer the potential for low temperature, neutral access to oxepin-2,3-oxides. The concerted ring opening of **1** to *Z*,*Z*-**3** was calculated by an earlier ab initio molecular orbital study (MP2/6-31G*//6-31G*) to have an activation energy of only 16.5 kcal/mol and to be exothermic by 17 kcal/mol, consistent with the reported transience of oxepin-2,3-oxide and its dimethyl derivative.[9] While reaction of hexamethylbenzene with DMDO[3] probably involved the first known reaction of an oxepin with a dioxirane, no attempt was made to isolate or observe the oxepin-2,3-oxide. Subsequent reaction of oxepin/benzene oxide with DMDO at low temperature, monitored by ^{1}H NMR spectroscopy, failed to provide spectra for the putative intermediate.[4] Reaction of 2,7-dimethyloxepin with MTDO in 1,1,1-trifluoroacetone at low temperature (ca. −80 °C), in the presence of added base (e.g., solid Na_2HPO_4 or 2,6-di-*tert*-butylpyridine), yielded a very minute concentration of an intermediate, tentatively assigned structure **7**, that disappeared when the NMR probe temperature was raised to ca. 0 °C.[5] Epoxidation using DMDO in acetone commenced around −30 °C, generating the identical intermediate that disappeared around 0 °C.[5] The very low concentration of the intermediate and one chemical shift coincidence were the reasons for our caution in assigning it structure **7**.[5]

Aside from its purely chemical interest, oxepin-2-oxide has been postulated by some to be the likely precursor of *Z*,*Z* muconaldehyde (*Z*,*Z*-**3**) in the P-450-mediated ring opening of benzene.[2,4,5] Muconaldehydes are known to react with DNA bases and are likely carcinogens.[10]

In principle, the oxepin-2,3-oxide nucleus can be stabilized through benzo-annelation at the 4,5-positions (see Scheme 3).[11] Epoxidation of 4,5-benzoxepin (**11**) should yield 4,5-benzoxepin-2,3-oxide (**12**), expected to exhibit enhanced thermodynamic and kinetic stability to concerted ring opening to *Z*,*Z*-**13** due to the benzene ring.[12] The present study compares the computed activation and rearrangement energies for ring opening of 4,5-benzoxepin-2,3-oxide (**12**) to *Z*,*Z*-**13** with the corresponding energies for the ring opening of oxepin-2,3-oxide (**1**) to *Z*,*Z*-muconaldehyde (*Z*,*Z*-**3**), concerted ring closures of *Z*,*Z*-**13** to 1*H*-2-benzopyran-1-carboxaldehyde (**14**) and *Z*,*Z*-**3** to 2*H*-pyran-2-carboxaldehyde (**15**) and corresponding ring opening to *E*,*Z*-**13** and *E*,*Z*-**3**, respectively. The annelated benzene ring in **14** makes



Scheme 3.

this structure a deep energy well on the rearrangement surface in contrast to **15**, which is higher in energy than *E*,*Z*-muconaldehyde (*E*,*Z*-**3**). Thus, reaction of **11** with an equimolar quantity of DMDO should provide **14** as the only stable product, in contrast with oxepin in which muconaldehydes (**3**) are isolated. Moreover, as noted below, reaction of 4,5-benzoxepin (**11**) with DMDO-d_6 in acetone-d_6 at −50 °C, observed via ^{1}H NMR, clearly produced 4,5-benzoxepin-2,3-oxide (**12**). Gradual warming and equilibration of the NMR probe indicated that starting around −20 °C, **12** was observed to rearrange quantitatively to **14** through the likely intermediacy of *Z*,*Z*-**13**. All traces of **12** were gone when the NMR probe temperature reached +10 °C.

An ab initio molecular orbital study provides some useful insights into the comparison of the stabilities of **1** and **12**. In the present work, optimization was performed employing DFT with the hybrid functional B3LYP[12] and the 6-31G* basis set.[13] This level of theory predicts an activation energy for epoxidation by DMDO of ethylene (17.9 kcal/mol) somewhat higher than the values predicted using the B3LYP and CCSD(T) methods in conjunction with the 6-311+G(2d,2p) basis set (13.1 and 13.7 kcal/mol, respectively).[14] Nonetheless, we employed this methodology throughout due to the size of the systems explored and our interest in relative numbers. The computed B3LYP/6-31G*/DFT energies of activation are 15.1 kcal/mol for formation of **1** from oxepin and 15.5 kcal/mol for formation 4,5-benzoxepin-2,3-oxide (**12**) from 4,5-benzoxepin (**11**) through reaction with DMDO. For comparison, the energy of activation for epoxidation of benzene by DMDO, at this level of theory, is 31.0 kcal/mol. This is consistent with the fact that benzene is inert to DMDO at ambient temperature.[8,15]

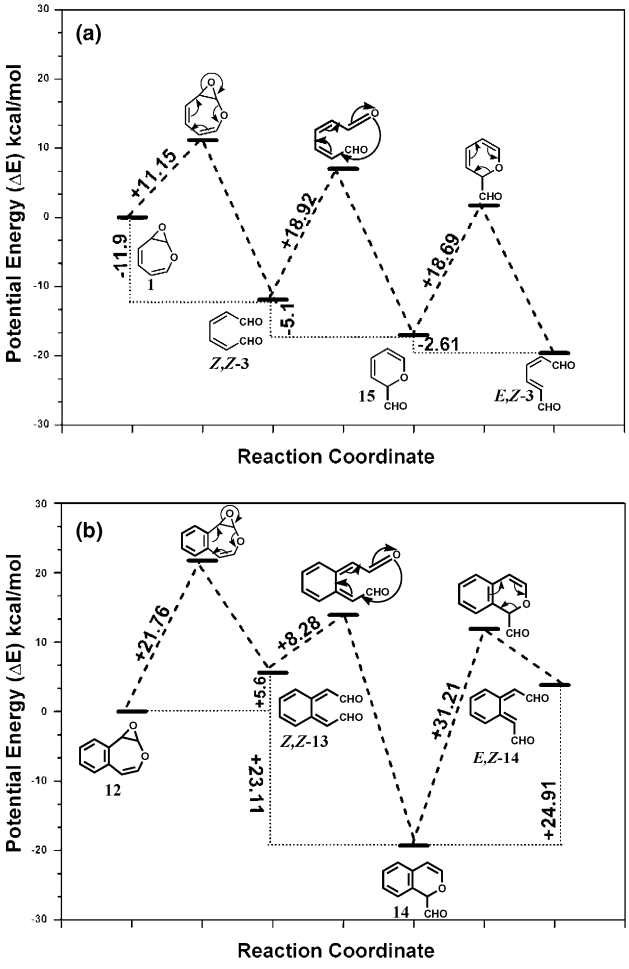


Figure 1. Calculated ring-opening rearrangement pathways for oxepin-2,3-oxides **1** and **12**.

The computed energies of activation for the ring opening isomerization of oxepin-2,3-oxide (**1**) to *Z*,*Z*-muconaldehyde (*Z*,*Z*-**3**), its ring closure to 2*H*-pyran-2-carboxaldehyde (**15**) and ring opening to *E*,*Z*-muconaldehyde (*E*,*Z*-**3**) and the corresponding pathway for 4,5-benzoxepin-2,3-oxide (**12**) are depicted in Figure 1. The effect of benzoannelation is clear: **1** produces muconaldehyde as the isomerization end-product while **12** should yield **14** as its end product.

Employing the methodology of Murray and Jeyaraman,[8a] reaction of 4,5-benzoxepin (**11**) (neat or in acetone) with an equimolar quantity of DMDO in acetone at room temperature (and lower temperatures with warm up to room temperature) provides 1*H*-2-benzopyran-1-carboxaldehyde (**14**). Evaporation of the solvent from the reaction mixture and analysis of the residue via ^{1}H NMR ($CDCl_3$) provides the following data: δ 5.35, d, $J = 0.6$ Hz, 1H; δ 5.74, d, $J = 5.8$ Hz, 1H; δ 6.68, d, $J = 5.8$ Hz, 1H; δ 7.0–7.5, m, 4H; δ 9.75, d, $J = 0.6$ Hz, 1H. These data are in excellent agreement with the literature data reported for **14**.[16] A completely unexpected finding was the formation of 4-methyl-4-hydroxy-2-pentanone (in a quantity significantly larger than the reactants): ^{1}H NMR ($CDCl_3$) δ 1.26, s, 6H; δ 2.18, s, 3H; δ 2.64, s, 2H; δ 3.81, br s, 1H). There was, apparently, aldol condensation of a tiny fraction of the solvent. There appears to be no precedent for this side reaction with the dioxirane/acetone reagent,[17] and we have not found this by-product in our other reactions with alkenes (e.g., *trans*-stilbene) and triphenylphosphine nor was it observed in the reaction of 2,7-dimethyloxepin with DMDO in acetone.[5] We note here that we always employed double-distilled acetone (starting with spectral grade) before preparing DMDO. NMR spectra of our DMDO solutions prior to their use as reagents (employed as one method for quantitating DMDO) did not provide evidence for acetone dimer. Similarly, gentle evaporation of double-distilled acetone to dryness and evaporation of the DMDO/acetone solution to dryness and uptake of any remaining residue in $CDCl_3$ failed to provide evidence for acetone dimer. Further investigation of this surprising result will be reported in the future.

Reaction was also performed at low temperature using DMDO-d_6 in acetone-d_6 according to the Murray–Jeyaraman procedure.[8a] 4,5-Benzoxepin (**11**) (5 mg) was placed in an NMR tube and pre-cooled in the probe to −50 °C. To this was added a less than equimolar amount of the deuterated dioxirane/acetone solution that had been pre-cooled to −78 °C. The initial ^{1}H NMR

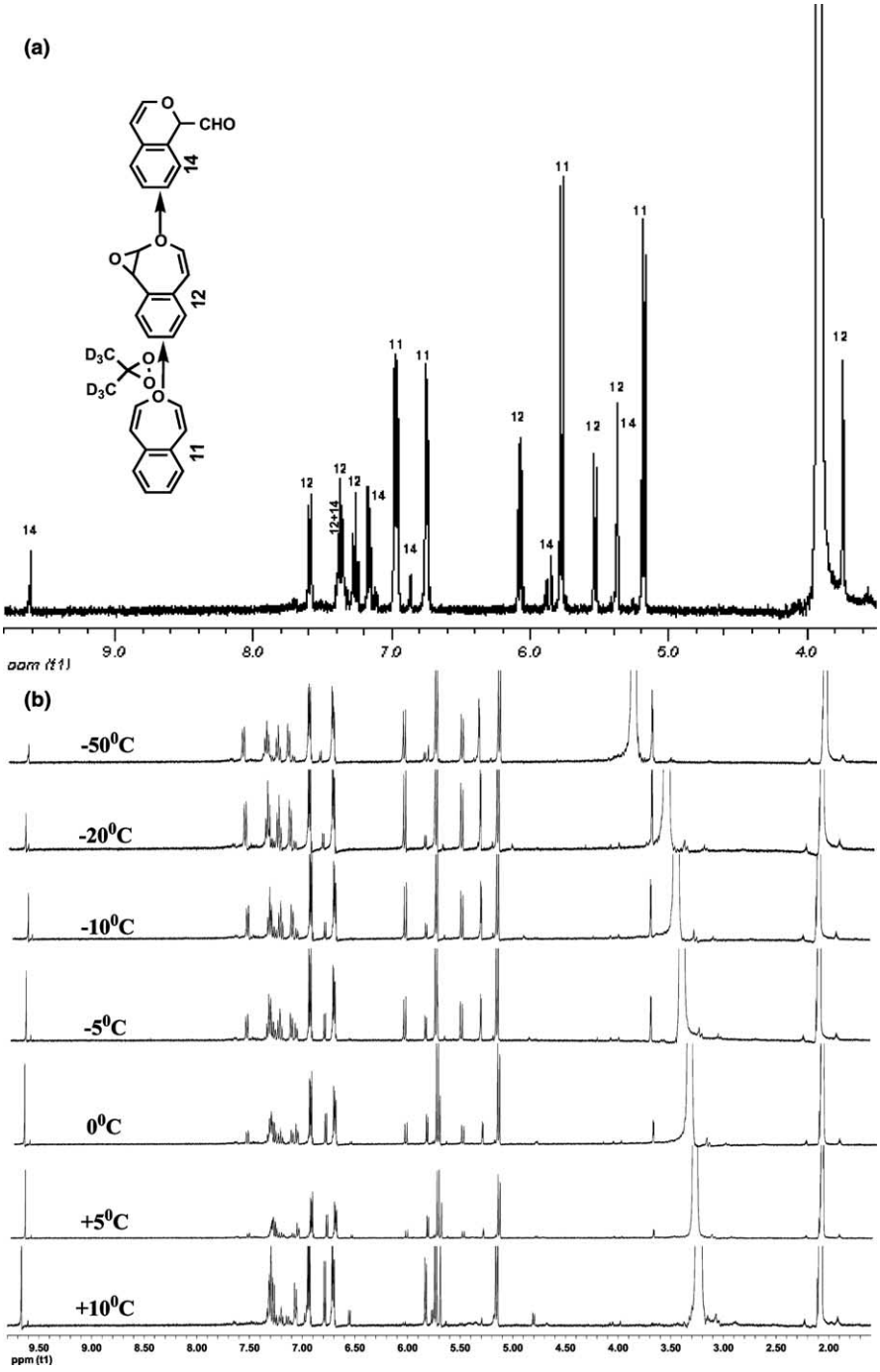
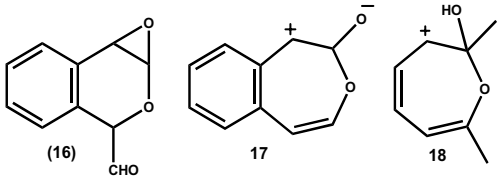


Figure 2. ^{1}H NMR spectrum (400 MHz) of reaction of DMDO-d_6/acetone-d_6 with 4,5-benzoxepin at −50 °C (top). Gradual warming of this solution led to rearrangement of 12 above −20 °C and its disappearance below +10 °C (typically ca. 5 min at each temperature).

spectrum (Fig. 2) showed the presence of some unreacted starting material (**11**) and a small amount of the stable product **14**. In this spectrum, the large doublets at δ 5.18, δ 5.77, δ 6.75 and δ 6.97 belong to the starting material 4,5-benzoxepin (**11**), and the small peaks at δ 5.36, d; δ 5.88, d; δ 6.87, d; 7.1–7.4, m; δ 9.62, s arise from the stable product 1*H*-2-benzopyran-1-carboxaldehyde (**14**). New signals are found at δ 3.74, d, $J = 2.6$ Hz, 1H; δ 5.37, d, $J = 2.6$ Hz, 1H; δ 5.54, d, $J = 8.0$ Hz, 1H; δ 6.08, d, $J = 8.0$ Hz, 1H; δ 7.15–7.55, m, 4H and are fully consistent with the ^{1}H NMR spectrum expected for **12**.[18] They are also consistent with the shifts of the corresponding signals reported earlier for **7**.[5] Upon warming in gradual increments of 10 °C, the NMR spectrum remained essentially unchanged up to −20 °C (Fig. 2). Upon increasing the probe temperature to −10 °C (Fig. 2), there is a clear decrease in the concentration of **12** and a corresponding increase in **14**. The spectrum of **12** is still present at +5 °C but disappears at +10 °C. There is some unreacted starting material (**11**) even at +10 °C. To this solution at +10°C, less than one half of an equivalent of DMDO-d_6 was added. The unreacted **11** remained and additional peaks appeared, which we tentatively assign to the

epoxide **16** (*syn* or *anti*): δ 4.07, d, $J = 2.5$ Hz, 1H; δ 5.30, br s, 1H; δ 5.64, d, $J = 2.5$ Hz, 1H; 7.2–7.7, m, 4H; δ 9.60, br s, 1H. There was also a much smaller peak at δ 9.77 along with other small, obscured peaks that are probably due to the minor stereoisomer of **16**. Clearly **14** is more reactive toward DMDO than is **11**.

In summary, we report the first unambiguous observation of an oxepin-2,3-oxide and its rearrangement to a stable, well-known isomer. The direct observation of the oxepin-2,3-oxide **12** and its conversion into the stable product **14** suggests that incubation of **11** with liver microsomal extract might provide **14** as an isolable product. The surprising finding that **12** decomposes below +10 °C despite having an activation barrier for concerted ring opening calculated to be 10 kcal/mol higher than that for **1**, suggests that this molecule has found a lower-energy rearrangement pathway. One possibility might be spontaneous heterolysis in the (albeit) moderately polar acetone solution to a minute quantity of **17**, a resonance stabilized, possibly homoaromatic, intermediate that rapidly rearranges to **13** and thence **14**. A minute quantity of zwitterion **17** could also function as the strong base, present in trace concentrations, that initiates the aldol condensation of the solvent acetone. The possible creation of a 'super base' in a neutral solution via an 'energy-pumping' epoxidation bears some resemblance to the incorporation of molecular oxygen to convert Vitamin K from a weak base to a 'super base' in nearly neutral media.[19] In contrast, it would appear that the thermal rearrangement of **7**, around 0 °C,[5] is concerted since the analogous zwitterion should not be as stable as **17**. The apparently rapid (at −80 °C) rearrangement of **7** in the presence of trace amounts of acid[5] suggests that its protonated form (**18**) also rearranges extraordinarily rapidly.



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