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# Insights into the Formation and Isomerization of the Benzene Metabolite Muconaldehyde and Related Molecules: Comparison of Computational and Experimental Studies of Simple, Benzo-Annelated, and Bridged 2,3-Epoxyoxepins

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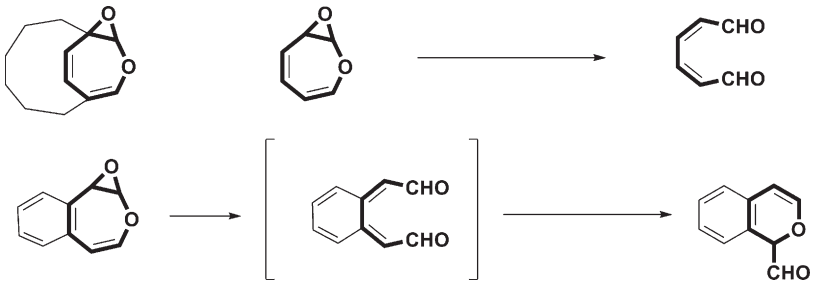


2,8-Dioxabicyclo[5.1.0]octa-3,5-diene ("2,3-epoxyoxepin") has been postulated as an intermediate in ring-opening metabolism of benzene. Density functional theory (B3LYP/6-31G*) is employed to study the activation and reaction energies for ring-opening isomerization of 2,3-epoxyoxepin, its 4,5-benzo derivative, and its 3,6-hexamethylene derivative. The results are compared with published experimental data. The markedly different fates of these three molecules suggest a means for testing the postulated metabolic pathway.

## Introduction

Only a very few derivatives of the 2,8-dioxabicyclo[5.1.0]octa-3,5-diene system (**1**) (herein referred to as "2,3-epoxyoxepin" for the sake of simplicity) have ever been isolated or characterized spectroscopically.[1] Yet 2,3-epoxyoxepin may well be the intermediate in ring-opening metabolism of benzene to muconaldehyde via cytochrome P450 monooxygenase. Our interest in 2,3-epoxyoxepin was inspired by the study by Davies and Whitham,[2] who recognized a potential route through epoxidation of benzene to benzene oxide (**2**), followed by epoxidation of its oxepin valence tautomer (**3**) to produce **1**, and then ring-opening to (*Z*,*Z*)-muconaldehyde (**4**) (Scheme 1). Benzene oxide and oxepin are nearly equienergetic, and the position of equilibrium is strongly solvent dependent.[3] Almost two decades earlier, Tomida and Nakajima[4] had suggested that **4** is a key intermediate en route to the benzene metabolite (*E*,*E*)-muconic acid (**5**) (Scheme 1). Convincing experimental evidence was provided by Goldstein, Witz and co-workers.[5] (*E*,*E*)-Muconic acid excreted in urine is commonly used to assess environmental exposure to benzene[6]

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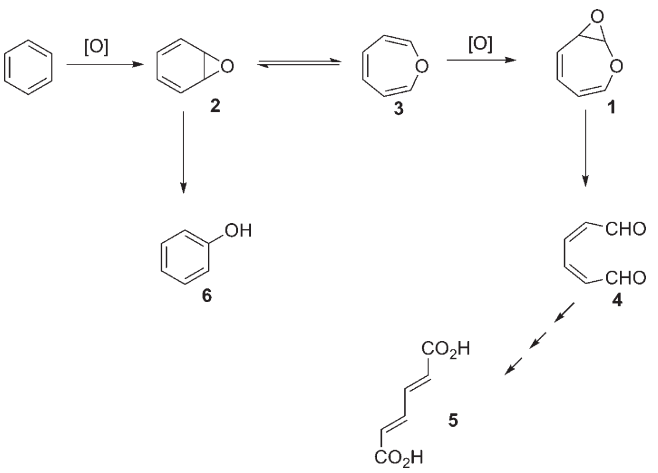
**SCHEME 1**




as part of the broader context of benzene metabolism.[7] (*E*,*E*)-Muconic acid typically comprises 10−20% of the benzene metabolites[6a−c] [the remainder being phenol (**6**) and metabolites derived from phenol]. Muconaldehyde is a very potent inhibitor of hematopoeisis (normal generation of blood cells).[7d] It reacts with glutathione, can cross-link proteins as well as DNA, and induces inhibition of gap junction intracellular communication through cross-linking of the protein connexin43.[8] Muconaldehyde is also a secondary air pollutant derived from ambient oxidation of benzene, and this aspect will be briefly addressed below.

As logical and "economical" (two consecutive monooxygenations) as the Davies and Whitham pathway appears, the mechanism for ring-opening metabolism of benzene remains uncertain. Benzene is metabolized by cytochromes P450 in the liver (primarily by CYP2E1). Evidence for the existence of benzene oxide (**2**), and its intermediacy en route to phenol is now quite strong.[9] However, pathways for ring-opening to muconaldehyde not involving the intermediacy of **2** have been suggested. One hypothesis is reaction of benzene with hydroxyl radical followed by oxygen involving Fenton-type chemistry.[10] Vapor-phase benzene does react with hydroxyl radical in the presence of oxygen to form muconaldehyde.[11] While benzene oxide/oxepin also reacts with hydroxyl radical to form muconaldehyde, it is unlikely that benzene oxide/oxepin is itself produced in the atmospheric chemistry of benzene.[12] If the hydroxyl radical was critical to the in vivo conversion of benzene to muconaldehyde, then a similar ring-opened byproduct of naphthalene might be present in the urine of mammals (including humans) exposed to naphthalene, since hydroxyl radical and oxygen also produce ring-opened products of naphthalene.[13] Naphthalene is about 20 times more reactive toward gas-phase hydroxyl radical than is benzene.[14] No ring-opened byproducts of naphthalene have been reported for mammals.[15] Metabolism occurs through 1,2-naphthalene oxide,[15] and the improbability of a 2,3-epoxyoxepin-type pathway for naphthalene has been discussed elsewhere.[16] Another suggested mechanism involves enzyme-catalyzed one-electron oxidation of the oxepin isomer to its radical cation en route to formation of muconaldehyde.[17]

While Davies and Whitham made a convincing case for the intermediacies of 2,3-epoxyoxepins, the acidic conditions characteristic of epoxidation reactions prior to the 1980s caused immediate rearrangements, and these investigators could neither isolate nor spectroscopically observe these intermediates.[2] Our early collaborative computational study, optimized at the 6-31G* level and including electron correlation (MP-2/6-31G*//HF6-31G*), predicted that ring-opening of the *trans-oid* conformer of **1** to (*Z*,*Z*)-muconaldehyde is exothermic by 17.0 kcal/mol with an energy of activation of only 16.5 kcal/mol.[18] Taking into account a calculated entropy of activation of −1.5 eu, the lifetime of **1** for (uncatalyzed) thermal (gas-phase) rearrangement was estimated at only 50 s at 0 °C.[18]

The development of dioxiranes as useful reagents during the 1980s[19] offered the opportunity to conduct epoxidations at low temperatures under neutral conditions. Reaction of 2,7-dimethyloxepin with dimethyldioxirane in an NMR tube at low temperature (ca. −40 °C) produced a very small quantity of the 2,7-dimethyl derivative of 2,3-epoxyoxepin (**7**), which rearranges to octa-3,5-diene-2,7-dione (**8**) starting at −10 °C (Scheme 2).[1f,2] A nearly simultaneous attempt to observe the parent molecule **1** was unsuccessful.[20] Clearly, muconaldehyde was formed via **1**, but only a small quantity of the isomeric "sym-oxepin oxide" (4,8-dioxabicyclo-[5.1.0]octa-2,5-diene) was observed via NMR starting around −40 °C, and this molecule rearranged to 4*H*-pyran-4-carbaldehyde starting at +10 °C.[20] *sym*-Oxepin oxide had previously been reported by Klein and Grimme[21] as well as Rastetter,[22]

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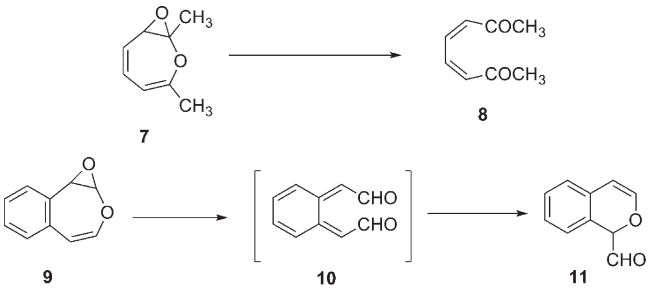
**SCHEME 2**

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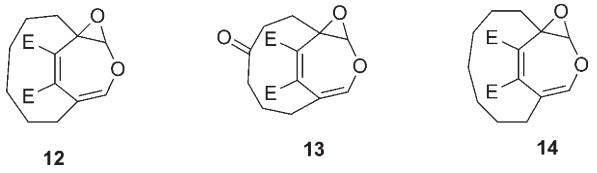


who subsequently investigated the relative mutagenicities of benzene oxides and oxepins.[23] Reasoning that the epoxidation of 4,5-benzoxepin should yield 4,5-benzo-2,3-epoxyoxepin (**9**), a molecule that might manifest an increased barrier to concerted ring-opening to the o-xylylene derivative **10**, this compound was synthesized in high yield using dimethyldioxirane-acetone at −50 °C.[1g] To our considerable surprise, **9** rearranged above −10 °C to yield **11** (Scheme 2). At the time, we were unaware of the series of bridged 2,3-epoxyoxepins (**12**−**14**, E = $CO_2CH_3$ or $CO_2C_2H_5$) reported by Tochtermann and co-workers (Scheme 3).[1a−e] Most strikingly, these compounds are thermally stable (melting points ranging from ca. 80 °C to ca. 100 °C) and, since they are synthesized using *m*-chloroperbenzoic acid, resist the very rapid acid-catalyzed rearrangements characteristic of species such as **7**.

The present investigation employs density functional theory to compare calculated thermochemical and kinetic data with selected experimental properties of the three structurally diverse 2,3-epoxyoxepins **1**, **9**, and **12** (E = H). In turn, another goal of this investigation is to help establish a framework for investigation of the metabolic ring-opening of benzene to muconaldehyde.

## Computational Methods

All geometries were optimized at the B3LYP/6-31G* level of theory as implemented in the Spartan 08[24] or in the Gaussian 03[26] suite of programs. All optimized structures, unless otherwise noted, were confirmed to be minima (zero imaginary frequencies) or transition states (one imaginary frequency) through their calculated energy second derivatives. The transition states were further characterized from intrinsic reaction coordinate (IRC) calculations and visualizing the imaginary normal mode. Relative energies and energies of activation refer to comparisons of calculated total energies. Zero-point energies and thermal corrections are available in the Supporting Information for this paper.

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The search for the ring-opening transition state for 2,3-epoxyoxepin (**1**) started with the calculated transition state for ring closure of 1,3*Z*,5*Z*,7-octatetraene file in the Spartan Database[25] and converting the terminal methylene groups to carbonyl oxygens and optimizing at the B3LYP/6-31G* level. The transition states for the benzo-substituted system (**9** → **10**) and the analogous ring-opening of the bridged system (**12**, E = H) were similarly located by initially building on to the transition-state structure obtained for the 2,3-epoxyoxepin system. Corresponding optimized calculations of 2,3-epoxyoxepin (**1**), its thermal ring-opening transition state, as well as the active conformer of (*Z*,*Z*)-muconaldehyde and the most stable conformers of (*Z*,*Z*)-muconaldehyde were performed using the PCM (polarizable continuum model) solvation by acetone. The analogous calculations were also performed for 4,5-benzo-2,3-epoxyoxepin (**9**). Searches for zwitterionic as well as singlet diradical intermediates for the ring-opening rearrangements of 2,3-epoxyoxepin (**1**) and its benzo derivative **9** were attempted employing UB3LYP/6-31G* calculations using Gaussian 03.[26]

The most stable cations derived from protonation of 2,3-epoxyoxepin were found in two ways: (a) the bond between C2 and the epoxy oxygen was broken and the proton attached to that oxygen, and (b) alternatively, the bond between C3 and the epoxy oxygen was broken, a proton attached to that oxygen. These species were optimized as above. The same procedure was performed on the most stable conformers of the 4,5-benzo-2,3-epoxyoxepin and 3,6-$(CH_2)_6$-2,3-epoxyoxepin. Single-point energy calculations, using the CCSD(T)/6-31G* level of theory, were performed on the two cations derived from protonation of 2,3-epoxyoxepin that had been optimized at the B3LYP/6-31G* level.

The search for the transition state corresponding to reaction of the 3,6-$(CH_2)_6$-bridged oxepin with dioxirane leading to **12** (E = H) started from the calculated transition state for reaction of dimethyldioxirane with 2-methyl-2-butene obtained from the Spartan Database.[25] B3LYP/6-31G* calculations of transition states involving epoxidation by dioxiranes reproduce quite well structures and energies achieved using higher levels of calculation.[27]

## Results and Discussion

**A. Relative Energetics of Corresponding 2,3-Epoxyoxepins and Ring-Opened Isomers.** Figure 1 depicts the activation and reaction energies for (gas-phase) isomerization of 2,3-epoxyoxepin (**1**) to (*Z*,*Z*)-muconaldehyde (**4**). The calculated transition state for this concerted electrocyclization reaction is depicted in Figure 2. The transition-state structure is virtually identical to that calculated previously using MP2/6-31G*//6-31G*.[18] It may be considered to be an 8$\pi$-Möbius-type aromatic transition state. The initially formed conformer

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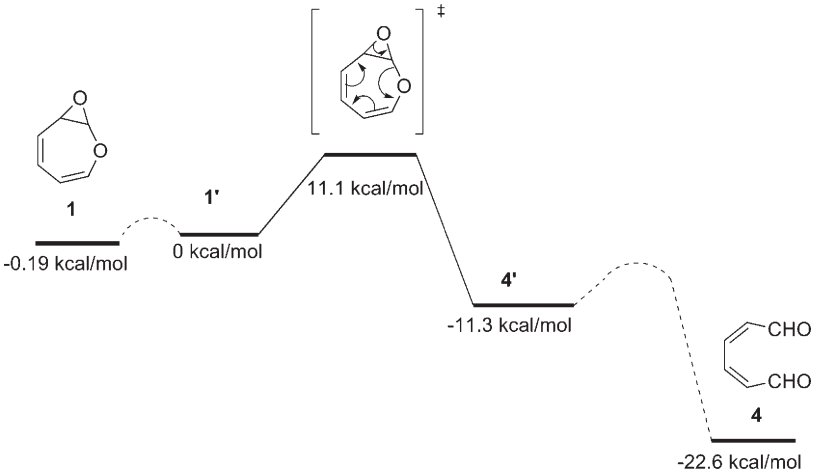


**FIGURE 1.** Calculated relative energies for isomerization of 2,3-epoxyoxepin (**1**) to (*Z*,*Z*)-muconaldehyde (**4**), setting the "active" conformation of 2,3-epoxyoxepin (**1′**) at 0.0 kcal/mol. Structure **4′** is the "active" conformation of (*Z*,*Z*)-muconaldehyde.

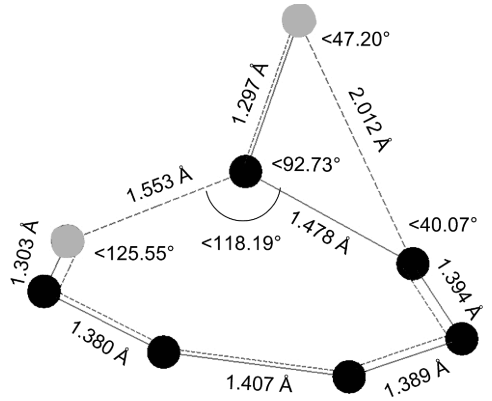


**FIGURE 2.** Transition-state model for ring-opening of 2,3-epoxyoxepin.

of (*Z*,*Z*)-muconaldehyde is less stable than the lowest energy conformer by 7.5 kcal/mol. Since the lowest energy conformer of 2,3-epoxyoxepin (**1**) is ca. 0.2 kcal/mol lower in energy than the "active" conformer (**1′**), the energy of activation is 11.3 kcal/mol. The overall reaction to form the most stable conformer of (*Z*,*Z*)-muconaldehyde is exoenergetic by 22.4 kcal/mol.

B3LYP/6-31G* calculations predict that the total energy of oxepin (uncorrected for zero-point energy and thermal energy) is 0.66 kcal/mol lower than that of benzene oxide. Experimental data (in $CF_3Br$/pentane, 2:1) indicate that oxepin is $1.7 \pm 0.4$ kcal/mol higher in enthalpy than benzene oxide, but 1.3 kcal/mol lower in free energy at room temperature due to its more positive entropy.[3] Higher order ab initio calculations with configuration interaction actually predict a very slightly higher total energy for oxepin.[28] 4,5-Benzoxepin is calculated to be 21.4 kcal/mol lower in energy than its benzene oxide tautomer, a value that far exceeds any computational uncertainties. Figure 3 depicts the relative energies for isomerization of 4,5-benzo-2,3-epoxyoxepin **9** to form **10** and then **11**. Figure 3 also depicts the relative energy of the transition state for ring-opening of **9** to *o*-xylylene derivative **10**. The calculated structure of the transition state is very similar to that of the parent (Figure 2) but with a shorter incipient carbonyl bond (1.265 Å) and other small changes reflecting a somewhat later transition state as expected in this endothermic reaction. Formation of **10** requires loss of the aromatic stabilization of **9**. The formation of "active" conformer **10′** is endoenergetic by 12.2 kcal/mol relative to "active" conformer **9′** and has a calculated energy of activation of 21.6 kcal/mol. The conversion of the most stable conformer of **9** to the most stable conformer of **10** is endoenergetic by 5.5 kcal/mol with an activation energy of 21.8 kcal/mol. However, the most stable conformer of *o*-xylylene derivative **10** is ca. 25 kcal/mol less stable than 3,4-benzo-2*H*-pyran-2-carbaldehyde (**11**), formed via subsequent Cope rearrangement.[1g] *o*-Xylylene derivative **10** furnishes an interesting contrast with muconaldehyde. The (*Z*,*Z*)- and (*E*,*Z*)-muconaldehydes are more stable than the 2*H*-pyran-2-carbaldehyde isomer that can interconvert with them.[29] Although the pyran isomer is a reasonable intermediate for this isomerization, catalyzed rearrangement is also a possibility for *Z*,*Z*- to *E*,*Z*-isomerization and seemingly a necessity for *E*,*Z*- to *E*,*E*-isomerization.[29a,30] In contrast, closure of the *o*-xylylene derivative regenerates a benzene ring and produces 3,4-benzo-2*H*-pyran-2-carbaldehyde (**11**) as the global minimum. Although a (gas-phase) barrier to ring-opening rearrangement of **9** is predicted to be 21−22 kcal/mol, this 2,3-epoxyoxepin also ring opened in solution at a low temperature (−10 °C) similar to that for the parent compound.[1g] PCM solvation by acetone lowered the calculated barrier to thermal rearrangement of **1** (by 1.3 kcal/mol) to 9.8 kcal/mol and rearrangement of **9** (by 1.6 kcal/mol) to 20.2 kcal/mol. Attempts to locate discrete epoxy-ring-opened zwitterion intermediates or singlet diradical intermediates computationally were unsuccessful. The parent optimizes to **4′** and the benzo derivative to **9′**. It is conceivable that the inner wall of the NMR tube employed in the study of **9**[1g] might have been slightly

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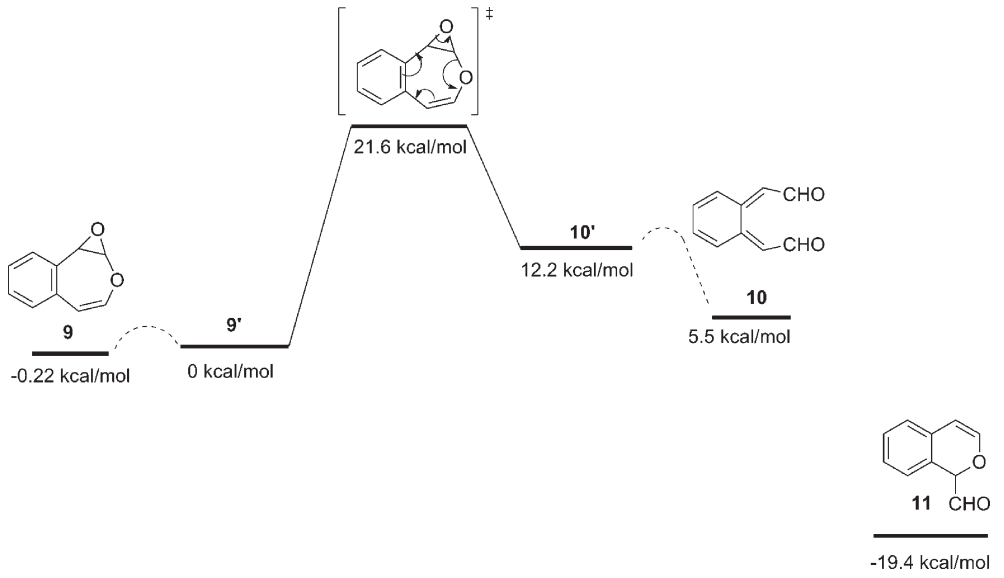



**FIGURE 3.** Relative activation energy and energy change for isomerization of 4,5-benzo-2,3-epoxyoxepin (**9**) to *o*-xylylene derivative **10** (via the corresponding "active" conformers **9′** and **10′**), subsequent rearrangement to the 2*H*-pyran-2-carbaldehyde derivative **11**, and the relative energy of the transition state for conversion of **9** to **10**.

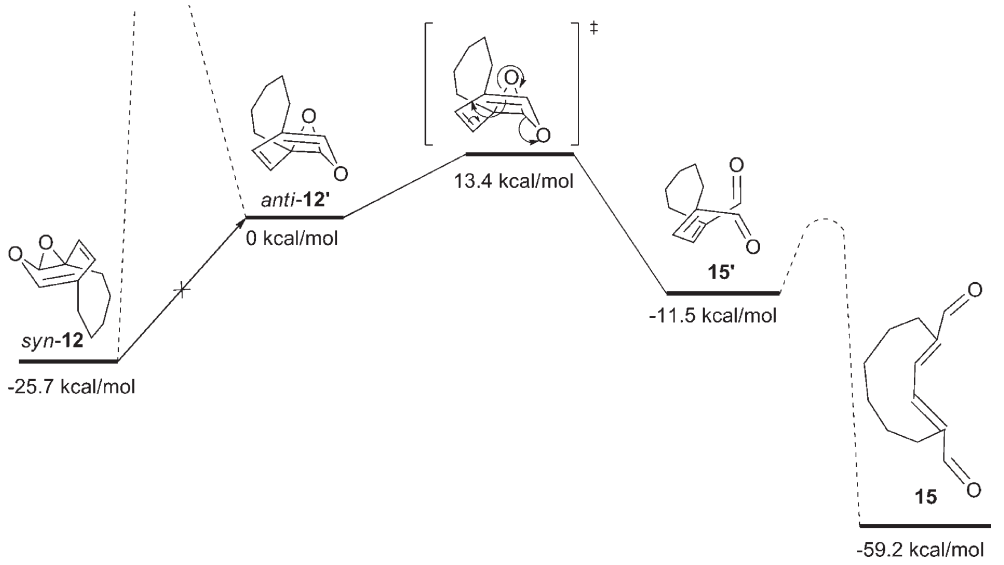


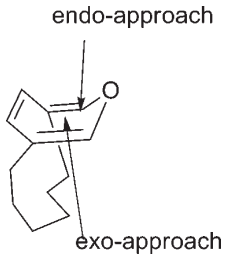

**FIGURE 4.** Depictions of the relative energies of the most stable conformer of the 3,6-$(CH_2)_6$-bridged-2,3-epoxyoxepin system, the "active" conformer leading to the ring-opening transition state, the transition state, the initial conformer of the product, and the most stable conformer of the product. [Due to steric constraints by the $-(CH_2)_6-$ bridge, the ring inversion required to convert the most stable conformer (*syn*-**12**) to the "active" conformer (*anti*-**12′**) cannot occur.]

acidic since a similar unanticipated glassware surface effect was reported for sym-oxepin oxide.[21]

The 3,6-bridged compounds **12** and **14** could, in principle, be metabolic products via consecutive mono-oxygenations of the highly strained [6]paracyclophane[31] and [7]paracyclophane,[32] respectively. Due to steric constraints introduced by the bridge, the oxepin tautomer is calculated to be 28.5 kcal/mol more stable than the benzene oxide. What is the source of the thermal stabilities of **12**−**14**? Figure 4 depicts relative energetics of the transition state for the ring-opening rearrangement of **12** to the cyclodeca-1,3-diene-1,4-dicarbaldehyde **15**. Starting from the "active" conformer **12′**, the energy of activation (13.4 kcal/mol) is not much different from that of 2,3-epoxyoxepin (**1**) itself, and the reaction is exothermic. The transition state is similar to that depicted in Figure 2. The hexamethylene bridge in this molecule prevents the epoxyoxepin ring from inverting; hence, we term the more stable structure the *syn*-stereoisomer. There are 14 low energy conformations for *syn*-**12**. The *anti*-stereoisomer is identical with the active conformer (*anti*-**12′**). The most stable *syn*-conformer is 25.7 kcal/mol lower in energy than the "active" conformer (*anti*-**12′**) (see Figure 4). This might at first suggest

(31) Kane, V. V.; Wolf, A. D.; Jones, M., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 2643–2644.
(32) Wolf, A. D.; Kane, V. V.; Levin, R. H.; Jones, M., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 1680.

**SCHEME 4**

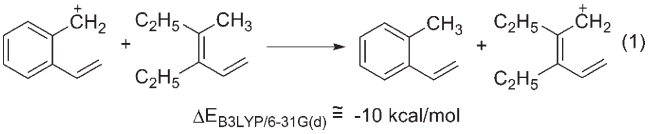



an activation energy for ring-opening rearrangement of **12** of ca. 39 kcal/mol or a bit higher. However, as noted above, the *syn*-**12** conformer cannot ring invert to form *anti*-**12**. *syn*-**12** is not only much more stable than the active conformer *anti*-**12′**, it is also formed much more rapidly via epoxidation (see below). In summary, once the most stable conformer (oxygens *syn*) is formed via kinetically favored epoxidation of 3,6-$(CH_2)_6$-oxepin, the hexamethylene bridge sterically prohibits inversion of the oxepin ring to form the active (oxygens *anti*) conformer. Therefore, the most stable conformer simply cannot transform to the favored transition state for thermal ring-opening isomerization. This accounts for the thermal stability of **12** despite its ring-opening being exoenergetic by 33−34 kcal/mol. Despite attempts to computationally "force" *syn*-**12** toward ring-opening rearrangement by stretching the appropriate bonds, no success was achieved with this approach.

The calculated transition state for *endo*-attack by dioxirane ($CH_2O_2$) is 7.8 kcal/mol lower in energy than that for the *exo*-attack. The hexamethylene bridge introduces steric hindrance to *exo*-attack on the boatlike oxepin ring in **12** (Scheme 4). Since the reactions are highly exothermic (−56.8 kcal/mol for *endo*-attack; −31.0 kcal/mol for *exo*-attack), involving early transition states, and dioxirane is sterically undemanding, less exothermic reactions involving more sterically demanding larger oxidizing agents should increase this bias. The sterically favored *endo*-attack forms the *syn*-oxygens stereoisomer (*syn*-**12**) which cannot conformationally interconvert to the *anti*-oxygen stereoisomer (*anti*-**12**), the one favored for facile thermal ring-opening.

**B. Structures of Protonated 2,3-Epoxyoxepins.** The experimentally observed stabilities of bridged 2,3-epoxyoxepins **12**−**14** to acid are in marked contrast to those of simpler systems such as **7**. In order to understand this property in some detail, investigations were initiated on protonated structures derived from **1**, **9**, and **12** (see **16**, **17**, and **20**−**23** in Scheme 5). The proton affinities of these three 2,3-epoxyoxepins to form the corresponding 2- and 3-hydroxy cations are listed in Table 1. These include zero-point energy and thermal corrections. Attempts to calculate the energy of the structure having the epoxy ring of **1** protonated and intact were unsuccessful since the ion spontaneously converges to structure **16** (hydroxyl group on C2). The isomer **17**, in which the hydroxyl group is attached to C3, is 11.12 kcal/mol less stable than **16**. However, it is clearly homoaromatic judging by its calculated structure (Figure 5). Specifically, the calculated C2 and C4 distance is only 1.590 Å. This is reminiscent of the homoaromatic cation **18** *postulated* by Klein and Grimme[21] to explain the exceedingly facile rearrangement of "sym-oxepin oxide" to 4*H*-pyran-4-carbaldehyde on contact with glass surfaces not pretreated with alkali. However, the calculated structure for the ion derived from protonation of "sym-oxepin oxide" appears to resemble **19** (calculated C3−C5 distance 2.49 Å) and thus not be the homoaromatic structure **18** postulated by Klein and Grimme.[21] The energy difference between **16** and **17** was also compared using single-point CCSD(T)/6-31G* calculations. The results favor **16** over **17** by 12.2 kcal/mol.

Protonation of 4,5-benzo-2,3-epoxyoxepin also favors the 2-hydroxy cation (**20**), calculated to be 8.2 kcal/mol more stable than the 3-hydroxy cation (**21**). The torsional angle in **16** between the C2−C3 bond and the C4−C5 bond is calculated at 3.3°. For the benzo derivative (**20**), the corresponding angle is 1.9°. Thus, ions **16** and **20** have extended, virtually coplanar conjugated $\pi$ systems. Although cation **17** is calculated to be homoaromatic, twisted overlaps mitigate the expected stabilization. The torsional angle between the C4−C5 and C6−C7 bonds in the protonated 2,3-epoxyoxepin cation **17** is calculated at 18.72°. Unlike the parent system, the corresponding ion (**21**) derived from the 4,5-benzo derivative, in which hydroxyl is on C3, has no significant homoaromaticity since the C2−C4 distance is calculated at 2.10 Å. This is reflected in the lower calculated proton affinity to form **21** (relative to **17** and **23**). This ion has a calculated 28.75° torsional angle, some 10° higher than in **17**, between the C4−C5 and C6−C7 bonds. The prediction that the proton affinity of **9** (to form **20**) is 6.3 kcal/mol less than the proton affinity of **1** (to form **16**) is readily understood through analogy furnished by eq 1:




The 3,6-$(CH_2)_6$-bridged derivative synthesized by Tochtermann's group was obtained using *meta*-chloroperbenzoic acid. It is thus relatively stable to acid unlike the parent system. The proton affinity for formation of the 2-hydroxy cation (**22**) is calculated to be nearly 18 kcal/mol less than that for the parent system and over 11 kcal/mol less than that for the 4,5-benzo derivative to form the corresponding 2-hydroxy cations (Table 1). Although **22** is a bridgehead carbocation, it is planar (sum of angles = 359.4°). However, the torsional angle between the C2−C3 bond and the C4−C5 $\pi$-system is 138.19° and between the C4−C5 and C6−C7 $\pi$-systems is 33.51°. We predict from the calculational results preferential formation of the 3-hydroxy cation (**23**) in contrast to the predictions for **1** and **9**. While this is mostly due to reduced conjugation in **22**, the additional α-alkyl substitution in **23** adds an additional stabilization (e.g., $[(CH_3)_2CH\text{-}(CH_3)_2]^+$ is 2 kcal/mol more stable than $[(CH_3CH_2CH_2)\text{-}C(CH_3)_2]^+$).[33] The calculated difference in (gas-phase) proton affinities between **1** and **12** is 6.6 kcal/mol, and this difference, albeit not very large, is consistent with the difference in stabilities in acidic medium although one might expect differences in solution to play a role as well. The 3-hydroxy

(33) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, 1–861. The same 2.0 kcal/mol difference is also reproduced by B3LYP/6-31G* calculations.

**SCHEME 5**

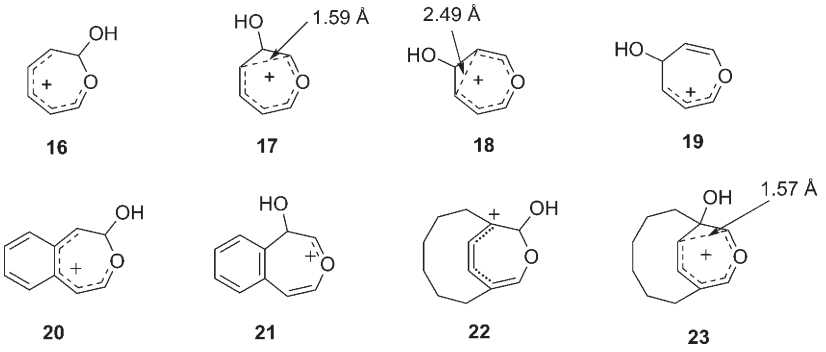



**TABLE 1. Calculated (B3LYP/6-31G*) Proton Affinities (PA) of Three 2,3-Epoxyoxepin Molecules To Form the 2-Hydroxy- and 3-Hydroxy-Type Cations (e.g., 16 and 17, Respectively)[a]**

| | proton affinity (kcal/mol) | |
|---|---|---|
| | 2-hydroxy cation | 3-hydroxy cation |
| 2,3-epoxyoxepin (**1**) | 231.2 (**16**) | 220.6 (**17**) |
| 4,5-benzo-2,3-epoxyoxepin (**9**) | 224.9 (**20**) | 216.7 (**21**) |
| 3,6-$(CH_2)_6$-2,3-epoxyoxepin (**12**, E = H) | 213.5 (**22**) | 224.6 (**23**) |

[a]The total energies are corrected for zero-point vibrational energies and thermal energies. For each compound, the higher proton affinity corresponds to the more stable cation.

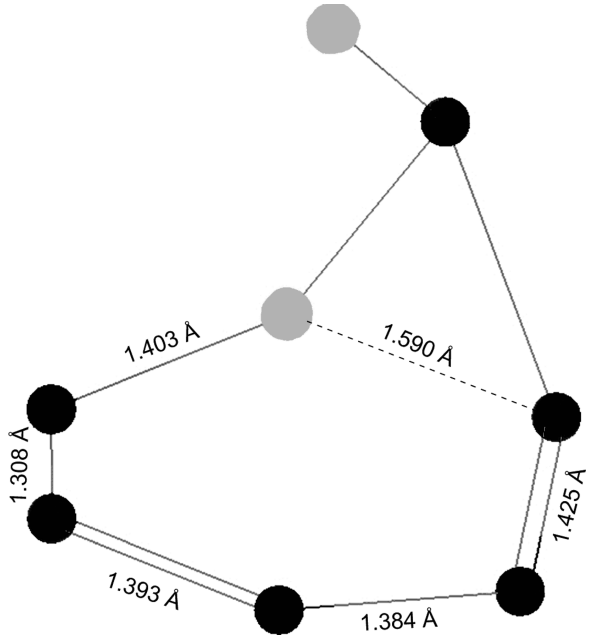



**FIGURE 5.** Structure of the homoaromatic cation (**17**) that could arise from protonation of **1**. This stabilized ion is calculated to be less stable than **16**.

cation (**23**) strongly resembles **17**, and its calculated C2−C4 distance is only 1.57 Å. Unlike **17**, the homoaromatic cation derived from the 3,6-$(CH_2)_6$-bridged species (**23**) may be accessible, since it is the more stable of the two isomeric ions.

## Conclusions

The thermal ring-opening isomerization of 2,3-epoxyoxepin to (*Z*,*Z*)-muconaldehyde is calculated to be exothermic with a low energy of activation (ca. 11 kcal/mol). The transition state is an aromatic Möbius 8 $\pi$ system in which the two oxygen atoms have an *anti* orientation. The ring-opening rearrangement of 4,5-benzo-2,3-epoxyoxepin to its *o*-xylylene-like isomer ("3,4-benzomuconaldehyde") is endothermic due to loss of aromaticity and has a considerably higher (21−22 kcal/mol) calculated energy of activation. The *o*-xylylene derivative **10** isomerizes to 3,4-benzo-2*H*-pyran-2-carbaldehyde (**11**), which is 25 kcal/mol more stable than **10** and 20 kcal/mol more stable than 4,5-benzo-2,3-epoxyoxepin (**9**). This relationship is in contrast to that in muconaldehyde where 2*H*-pyran-2-carbaldehyde is higher in energy than the ring-opened isomers and is a reasonable intermediate for isomerization of (*Z*,*Z*)-muconaldehyde to (*E*,*Z*)-muconaldehyde. In spite of the prediction of a significantly higher barrier to thermal ring-opening of 4,5-benzo-2,3-epoxyoxepin, in acetone solution the molecule ring opened rapidly at about −10 °C, remarkably close to the temperature at which the parent ring opened, en route to forming **11**. Calculations involving PCM solvation by acetone only slightly lower the concerted ring-opening barriers of **1** and **9**. Attempts to locate discrete zwitterionic and singlet diradical intermediates for these ring-opening isomerizations were unsuccessful. It is possible that the inner surface of the glass NMR tube employed in the generation of **9** had acidic sites. This will be investigated further using an NMR tube prewashed with base.

Derivatives of 2,3-epoxyoxepin in which the 3- and 6-positions are bridged by hexamethylene or heptamethylene groups have very different reaction patterns relative to the parent compound. The 3,6-bridged species do not rapidly rearrange under acidic conditions. They are thermally quite stable, with melting points in the 80−100 °C range. The bridge forces the seven-membered oxepin ring to adopt a fairly rigid boat-like structure with the bridge covering part of the *exo*-surface of the ring. Epoxidation (e.g., by dioxirane) is strongly favored from the *endo*-surface which has the effect of fixing the oxygens in the resulting 2,3-epoxyoxepin derivative into a rigid *syn* relationship. Since the transition state for concerted ring-opening isomerization requires the oxygens to be *anti*- the molecule resists thermal ring-opening. The kinetically disfavored isomer of the 3,6-bridged molecule, in which the two oxygens are *anti*, is calculated to be 25−26 kcal/mol higher in energy than the *syn* isomer. Its activation barrier (13−14 kcal/mol) is similar to that of the parent (11 kcal/mol). However, since the *syn*-isomer is ca. 26 kcal/mol more stable, the activation barrier for ring-opening would probably be in excess of 40 kcal/mol, if the molecule

was in fact capable of inverting. The $-(CH_2)_6-$ as well as the $-(CH_2)_7-$ bridges sterically prohibit this inversion.

Attempts to protonate the epoxy ring computationally in the three epoxyoxepins led to the ring-opened hydroxyl carbocations. The highest proton affinity was calculated for the parent molecule **1**. Protonation of **1** and the 4,5-benzo derivative **9** led to the corresponding 2-hydroxy carbocations **16** and **20**, respectively. However, formation of the 2-hydroxy carbocation (**22**) derived from the 3,6-bridged compound **12** is nearly 18 kcal/mol less favorable than the corresponding ion for **1** and over 11 kcal/mol less stable than that derived from **9**. Protonation of **12** favors formation of the 3-hydroxy carbocation (**23**), and its formation corresponds to a proton affinity 6−7 kcal/mol lower than that of **1**. This is consistent with the stability of **12** to acid.

It is worth noting that this calculational study suggests a means for further investigation of the epoxyoxepin hypothesis for cytochrome P-450-mediated ring-opening of benzene. If this mechanism is operative and all three substrates metabolized, then one would expect 2,7-dimethyloxepin to yield octa-3,5-diene-2,7-dione (**8**), 4,5-benzoxepin to yield 3,4-benzo-2*H*-pyran-2-carbaldehyde (**11**), and 3,6-hexamethylene oxepin to yield the bridged 2,3-epoxyoxepin **12** (E = H).

**Acknowledgment.** We gratefully acknowledge preliminary studies by Dr. Dhananjaya Nauduri and helpful discussions and advice from Professor Richard Johnson, University of New Hampshire.

**Supporting Information Available:** Total energies, full geometries, zero point energies, and thermal corrections for all structures. This material is available free of charge via the Internet at http://pubs.acs.org.