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Conformation and Cope Rearrangement of *sym*-Oxepin Oxides

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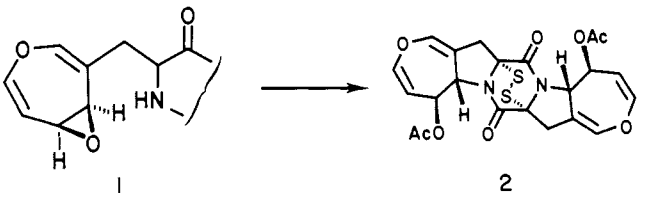
Abstract: The synthesis of a homologous series of transoid, bridged *sym*-oxepin oxides (**10a–c**) is described. The lower homologues, **10a,b**, do not undergo facile Cope rearrangement to the *sym*-oxepin oxides **15a,b**. The generation of transoid **10c** led rapidly to the production of the Cope rearrangement product **15c**. The differing reactivity in the series **10a–c** is attributed to the inability of **10a,b** to interconvert with their cisoid isomers, **14a,b**. The production of **15c** is thought to occur via ring inversion of transoid **10c** to cisoid **14c**, followed by rapid Cope rearrangement (**14c** → **15c**). Under forcing conditions **10a,b** undergo epoxide opening and a subsequent rearrangement.

In an elegant scheme Neuss and co-workers in 1968 postulated[1] the intermediacy of an oxepin oxide (**1**, Scheme I) during the fungal biogenesis of the aranotins (e.g., acetylaranotin, **2**). Thus, it was suggested, the stereochemistry of the dihydrooxepin moiety of the aranotins is established by intramolecular displacement at carbon with Walden inversion in enzyme-bound epoxide **1**.

The first syntheses of an oxepin oxide were communicated by Klein and Grimme,[2a] and by us[2b] in 1974–1975. Subsequently, we detailed[3] our conversion of benzene oxide oxepin to *sym*-oxepin oxide (**3**, R = H, Scheme II), and studied the conformation and Cope rearrangement of **3** (R = H) by ^{1}H NMR spectroscopy.[4] Other studies revealed the Cope rearrangement of a methylated derivative[5] and helped define the scope[6] of our synthetic approach to oxepin oxides. Further, we reported the synthesis of the bridgehead diene **10a**[7] (Scheme IV) and characterized a derivative of **10a** by X-ray crystal analysis.[8]

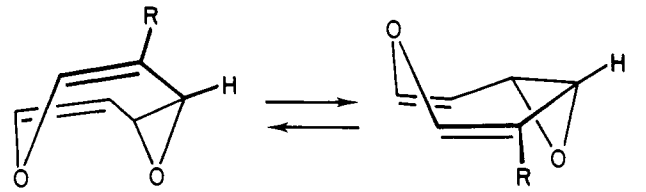
The possible intermediacy of an enzyme-bound oxepin oxide in biogenesis (Scheme I) raises an intriguing question of stereochemistry. A priori one must consider two stereochemical outcomes for the Cope rearrangement of a chiral oxepin oxide (**4**, Scheme III). In principle, **4** could interconvert, via Cope rearrangement, with its diastereomer **5** (**5** ≠ **4**) or with its rotamer **6** (**6** = **4**). The interconversion **4** ⇌ **5** would proceed via a transition state resembling cisoid conformation **3a** (Scheme II); the degenerate rearrangement **4** ⇌ **6** would proceed via a transoid transition state[9] (cf. **3b**, Scheme II). Thus, the stereochemical integrity of an intermediate, chiral oxepin oxide would depend on the rate and the geometrical requirements of the Cope rearrangement. Herein we report that *oxepin oxides locked in transoid conformations do not undergo facile Cope rearrangements*, in sharp contrast to conformationally mobile oxepin oxides.

Scheme I



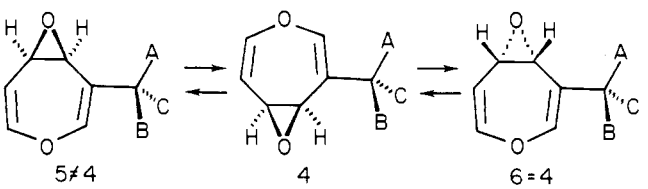
1 2

Scheme II



3a 3b

Scheme III



5≠4 4 6=4

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Synthesis and Reactivity Studies

Strategy. The bridged arene oxide-oxepin systems **8** ⇌ **7** (Scheme IV) were reported by Vogel and Günther.[10] The lower homologues exist as valence tautomers **8a** and **8b**, and lack the characteristic orange color of oxepins (see valence tautomers **7a** and **7b**). The spectral properties of the highest homologue indicate the presence of an arene oxide-oxepin mixture with comparable concentrations of the components, **7c** ⇌ **8c**. Thus, the strain associated with the bridgehead double bonds of valence tautomers **7a–c** influences the position of the equilibrium **7** ⇌ **8**.

Application of our arene oxide → oxepin oxide conversion[2b,3,5,7] using **8a–c** as starting materials would produce oxepin oxides **10a–c** (Scheme IV). Ample precedent[4,5] indicated that nitrogen extrusion from azo diepoxides **9a–c** would occur with participation of only the epoxide anti fused to the azo bridge. The oxepin oxides, so produced, would be generated in transoid conformations (compare **10a–c** with **3b**). At least in the lowest homologue, **10a**, the methylene bridge would prevent interconversion of transoid **10a** with its cisoid isomer **14a** (Scheme V). The conversion **10a** → **14a** would require passage of the bis enol ether oxygen through the six-membered ring formed by the methylene bridge, the bridgehead carbons, and the ether oxygen. Lengthening of the methylene bridge, at some point, would allow passage of the ether oxygen through the bicyclic framework interconverting transoid (**10**) and cisoid (**14**) conformers. By this strategy similarly substituted conformationally rigid and conformationally mobile oxepin oxides could be made. The rigid lower homologue(s), e.g., **10a**, would display properties attributable to the transoid geometry.

With regard to Cope rearrangement, the strain of the bridgehead double bonds would *thermodynamically*, if not kinetically, favor rearrangement of the lower homologues **10a,b** to the Cope rearrangement products **15a,b** (Scheme V). Thus, the same thermodynamic factors which drive **7a,b** toward **8a,b** (Scheme IV) would favor the rearrangement **10a,b** → **15a,b**.[11]

In order to examine the conformational requirements for the Cope rearrangement of oxepin oxides, we have undertaken the syntheses of **10a–c**. Our results follow.

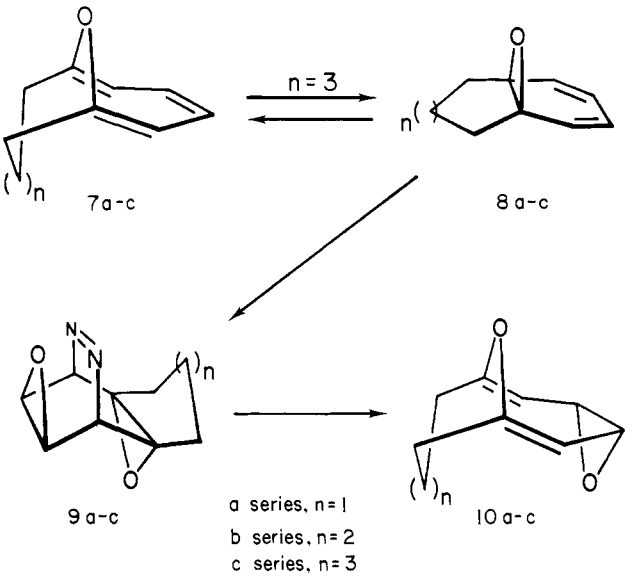
Oxepin Oxide 10a, *n* = 1.[7] Azo diepoxide **9a** (Scheme IV) is thermally labile but may be characterized by ^{1}H NMR at −40 °C. Brief warming of the NMR solution to ambient temperature leads to nitrogen extrusion and the quantitative (^{1}H NMR) generation of **10a**. A similar sequence from *syn*-2-hydroxyindan 3a,7a-oxide[12] (i.e., hydroxy-substituted **8a**) produced a substituted derivative of **10a**,[8] for which an X-ray crystal analysis clearly revealed a transoid conformation and twisted bridgehead double bonds.

At ambient temperature, conformationally mobile oxepin oxides[4,5] undergo rapid Cope rearrangement.[13] Strained, transoid oxepin oxide **10a** is not observed to rearrange to the Cope product **15a** (Scheme V), however, under a variety of thermal conditions. The cis divinyl oxirane, **10a**, is isolable and readily purified to analytical purity by sublimation. Under forcing conditions (pyrolysis or acid) **10a** rearranges in low yield to the *p*-quinol **13a** (Scheme VI).

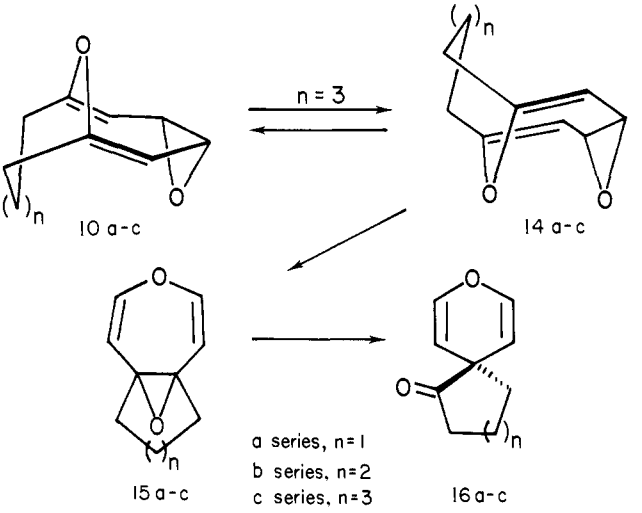
Oxepin oxide **15a**, though apparently inaccessible via Cope rearrangement of **10a**, is readily generated from indan 5,6-oxide (**17**, Scheme VII), via azo diepoxide **18**. Nitrogen extrusion from **18**, with participation of the anti-fused epoxide, produces **15a** directly. Oxepin oxide **15a** shows no tendency (^{1}H NMR) to interconvert with transoid **10a** or cisoid **14a**. Upon treatment with trace acid **15a** quantitatively ring contracts to spiro ketone **16a** (Scheme V).

Oxepin Oxide 10b, *n* = 2. Azo diepoxide **9b** (Scheme IV) in solution ($CDCl_3$) extrudes nitrogen at ambient temperature over a period of several hours with the quantitative (^{1}H NMR) generation of oxepin oxide **10b**. Alternatively, sublimation of solid **9b** yields white, crystalline **10b**.

Scheme IV



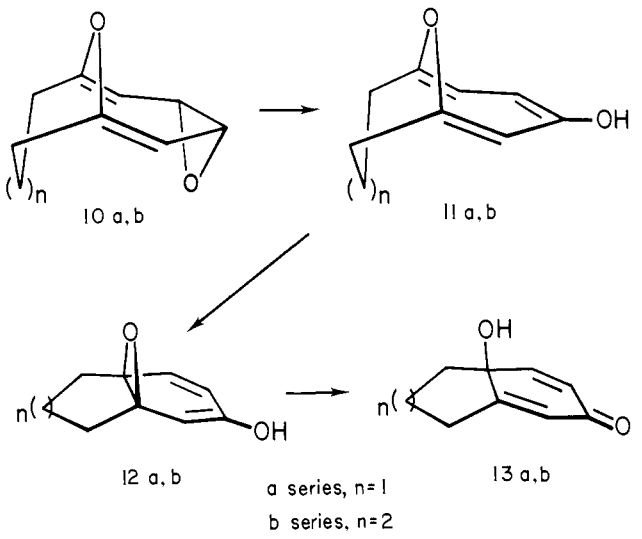
Scheme V



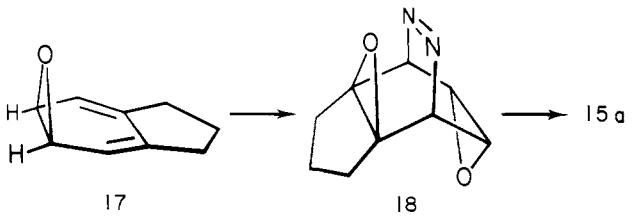
Stable, transoid oxepin oxide **10b** is not observed to rearrange to Cope product **15b** (Scheme V); under forcing conditions (pyrolysis or acid) **10b** rearranges in moderate yield to *p*-quinol **13b** (Scheme VI).

Oxepin Oxide 10c, *n* = 3. In sharp contrast to the above cases (**9a,b**) nitrogen extrusion (pyridine-d_5, 60 °C, 2 h) from azo diepoxide **9c** (Scheme IV) gives the Cope rearrangement product, oxepin oxide **15c** (Scheme V), in quantitative yield (^{1}H NMR). The strongly precedented[4,5] participation of an anti-fused epoxide in nitrogen extrusion demands the intermediacy of transoid **10c** in the nitrogen extrusion from azo diepoxide **9c**. At no point during the nitrogen extrusion process, however, are seen ^{1}H NMR absorptions attributable to transoid oxepin oxide **10c** or its cisoid conformer **14c**. Intermediates **10c** and/or **14c** are effectively trapped by nitrogen extrusion in the presence of trace acid ($MeSO_3H$). Under these conditions the ring contraction product from **10c**/**14c**, aldehyde **19** (Scheme VIII), is formed, accompanied by the ring contraction product from **15c**, spiro ketone **16c** (Scheme V) (**15c**:**16c** = 1:1). Throughout the extrusion process from azo diepoxide **9c**, in the presence of trace acid, aldehyde **19** and spiro ketone **16c** are formed at the same rate, implicating the same rate-deter-

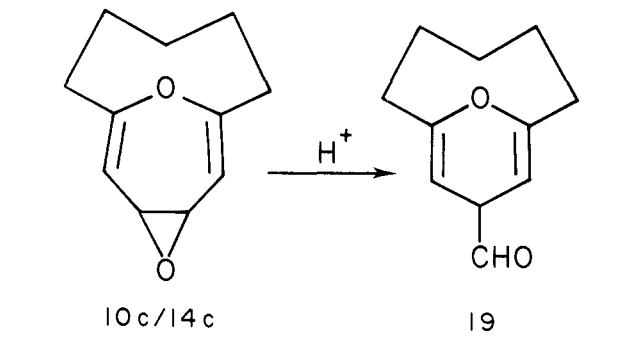
Scheme VI



Scheme VII



Scheme VIII



mining step (nitrogen extrusion) during their formation. By contrast, addition of acid *after* formation of Cope product **15c** gives rise only to spiro ketone **16c**.

Discussion

Conformation and Cope Rearrangement. An examination of molecular models readily shows the origin of the kinetic stability of transoid oxepin oxides **10a,b**. Dreiding models show the dihedral angle between the epoxide C–H bonds and the vicinal, vinyl C–H bonds to be approximately 65° in transoid **10a** or **10b**. X-ray crystal analysis of a derivative of **10a**[8] revealed a dihedral angle of 69.4° between the corresponding C–H bonds. By contrast, a model of cisoid **14a,b** shows the epoxide C–H bonds and the vinyl C–H bonds to be more nearly coplanar, with a dihedral angle of approximately 15°. In the transition state for Cope rearrangement, double-bond character must develop between the epoxide carbons and the adjacent vinyl carbons. A cisoid transition state, with more nearly coplanar substituents on the developing double bond, will be lower in energy than a transoid transition state, with severely twisted double bonds.[14] The twist of the ground-state double bonds of **10a,b**[8] is not sufficient to compensate for the higher energy transoid transition state; consequently **10a,b** are *kinetically* stable.

A similar effect of conformation was shown by Grimme[15] in the Cope rearrangement of a series of *cis*-bicyclo[6.1.0]-nona-2,6-dienes, in which steric inhibition of the reactive conformation for Cope rearrangement led to higher activation barriers for rearrangement. In all cases studied, though, rearrangement occurred via cisoid transition states. The prediction by Doering and Roth[14] of the facility of Cope rearrangements of homotropilidenes (the hydrocarbon analogues of oxepin oxides) via cisoid transition states has been borne out in several other cases.[16] Of particular interest are the bridged, fixed cisoid homotropilidenes[17] such as bullvalene, barbaralane, and semibullvalene, which undergo rapid, degenerate Cope rearrangements.

The failure to observe Cope rearrangement of oxepin oxides **10a,b** is attributed to the high barrier for ring inversion of **10a,b** to the cisoid isomers **14a,b**. That the bis enol ether oxygen of **10c** should be capable of passage through the eight-membered ring formed by the bridging methylene groups, the bridgehead carbons, and the ether oxygen is readily appreciated from inspection of Dreiding molecular models. Further, the passage of the ether oxygen through the eight-membered ring of **10c** is precedented by the racemization of *trans*-cyclooctene,[18] which occurs by passage of a vinyl C–H bond through the eight-membered ring of the cycloalkene.

The quantitative rearrangement of **10c** ⇌ **14c** to **15c** strongly points to kinetic rather than thermodynamic factors controlling the stability of the lower homologues **10a,b**. Thus, a release of strain would accompany the rearrangements **10a,b** → **15a,b** were it not for the kinetic barrier imposed by ring inversion. This view is further supported by the thermodynamic stability of **15a** produced via the reactions of Scheme VII. A similarly substituted epoxide, 4,5-dimethyloxepin oxide,[5] undergoes quantitative Cope rearrangement to 2,7-dimethyloxepin oxide. Although **15a** can easily adopt the cisoid conformation, Cope rearrangement to **14a** would introduce the strain associated with the bridgehead double bonds.

Rearrangements Induced by Epoxide Cleavage. The rearrangements of transoid oxepin oxides **10a,b** to *p*-quinols **13a,b** are depicted in Scheme VI. The enols **11a,b** may be derived via epoxide to ketone isomerization of **10a,b**. Oxepin to arene oxide valence tautomerization (**11a,b** → **12a,b**, cf. Scheme IV) would release the bridgehead strain of oxepins **11a,b**. Finally, enol-assisted epoxide opening of **12a,b** would produce *p*-quinols **13a,b**.

In contrast to the relatively acid stable **10a** (see Experimental Section) kinetically invisible **10c** and/or its conformer **14c** are rapidly trapped by acid. The ring contractions of **10c** and/or **14c** and of **15a,c** follow the pattern seen in unbridged systems[2,3,5] in which a high degree of bis enol ether lone pair participation renders the epoxides highly labile to acid. The conformational mobility of **10c** and **14c** allows the ring flattening which must accompany oxygen lone pair participation. Similar acid lability was used to trap kinetically invisible 4,5-dimethyloxepin oxide prior to its Cope rearrangement to 2,7-dimethyloxepin oxide.[5]

Biological Implications. The Cope rearrangement of a chiral, enzyme-bound oxepin oxide (**4**, Scheme III) would most certainly lead to a loss of stereochemical integrity of the intermediate via the interconversion **4** ⇌ **5**. Short of releasing the presumably undesired diastereomer (e.g., **5**) an enzyme might circumvent the problems posed by the interconversion **4** ⇌ **5** in several ways. Conversion of oxepin oxide **4** to a product of epoxide opening (see Scheme I) could be much faster than stereochemical scrambling by Cope rearrangement.[19] Alternatively, an enzyme could preferentially bind or induce further reaction of one diastereomer, thereby driving the equilibrium **4** ⇌ **5** in either direction. Finally, preferential binding and

reaction via the transoid conformation of **4** would totally prevent Cope rearrangement and the consequent loss of stereochemical integrity.

Experimental Section

^{1}H NMR spectra were obtained on a Perkin-Elmer Hitachi R-20 or R-24B (60 MHz) and ^{13}C NMR spectra (15 MHz) on a JEOL FX-60 Q spectrometer. Mass spectra were determined on a CEC 110B Mattauch-Herzog (Du Pont Instruments) high-resolution mass spectrometer and infrared spectra on a Perkin-Elmer 567 grating infrared spectrophotometer. Melting points are uncorrected and were obtained in open capillary (Mel-Temp instrument). All glassware used for the preparation or handling of the conformationally mobile, acid-labile oxepin oxides was base treated.[3] Chlorinated solvents were routinely purified by passage through basic alumina immediately prior to use; THF was distilled from sodium-potassium benzophenone ketyl.

Preparative work with arene oxides and conformationally mobile oxepin oxides is often complicated by the extreme lability of the materials. Attempts to isolate certain arene oxides (vide infra) may lead to violent, exothermic decomposition; isolation of oxepin oxides may lead to glass-surface-catalyzed rearrangement. Oxepin oxides and their pyran ring-contraction products are oxygen sensitive. Where isolation was shown to be impractical, we have characterized these materials as fully as possible in solution.

Syntheses of Azo Diepoxides 9a–c. The syntheses of **9a–c** parallel our synthesis of the azo diepoxide precursor of the parent compound, *sym*-oxepin oxide.[2b,3] The route to **9a**, previously communicated,[7] is detailed in the microfilm supplement[20] to this paper; the routes to **9b,c** are analogous.

Preparation of Oxepin Oxide 10a (n = 1). A suspension of the cuprous complex of **9a**[20] (1.6 g, corresponding to 8.31 mmol of adduct diepoxide) in CH_2Cl_2 (5.0 mL) was cooled and treated with 20% (w/v) aqueous NH_3 (5.0 mL) as described in ref 3 and 20. The mixture was warmed to ambient temperature, resulting in vigorous N_2 evolution, and the organic and aqueous layers were separated. The aqueous layer was further extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and rotary evaporated to solid oxepin oxide **10a**. Sublimation (60 °C, 0.05 mmHg) yielded white prisms (0.764 g, 61% based on adduct diepoxide): mp 67–69 °C; ^{1}H NMR ($CDCl_3$) δ (Me_4Si) 2.33 (m, 6 H), 3.83 (AA′XX′, 2 H), 5.00 (AA′XX′, 2 H); ^{13}C NMR ($CDCl_3$) δ (Me_4Si) 29.56 (t, $J \simeq 130$ Hz), 30.21 (t, $J \simeq 130$ Hz), 53.29 (d, J = 175 Hz), 107.86 (d, J = 164 Hz), 169.11 (s); IR ($CDCl_3$) 1676, 1662, 1396, 1101 cm^{-1}; UV (MeCN) λ_{max} (shoulder) 230 nm (ϵ 8.5 × 10^2); (EtOH) λ_{max} 231 nm (ϵ 5.4 × 10^2); exact mass calcd for $C_9H_{10}O_2$ m/e 150.068, found 150.070. Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 72.01; H, 6.61.

Preparation of Oxepin Oxide 15a. The starting material needed for preparation of oxepin oxide **15a** was the previously unreported indan 5,6-oxide (**17**) which we prepared by a modification of Vogel and Günther's procedure[10] for indan 3a,7a-oxide (**8a**). Thus, the dihydroindan[21] was first brominated, then epoxidized; the reversal of steps from the procedure for **8a** gives the correct position for the epoxide in the dibromo epoxide precursor for **17**. Details of our synthesis of **17** and its conversion to oxepin oxide **15a** are given in the microfilm supplement.[20] Data for **15a**: ^{1}H NMR (py-d_5) δ (Me_4Si) 1.50 (m, 6 H), 5.16 (d, J = 7 Hz, 2 H), 6.29 (d, J = 7 Hz, 2 H); IR (py-d_5) 1670, 1650 cm^{-1}.

Partitioning of the pyridine-d_5 NMR sample of **15a** between 5% HCl and $CDCl_3$ and separation and drying of the organic phase resulted in complete conversion to spiro ketone **16a**: ^{1}H NMR ($CDCl_3$) δ (Me_4Si) 1.90 (m, 4 H), 2.23 (m, 2 H), 4.52 (AA′XX′, 2 H), 6.38 (AA′XX′, 2 H); ^{13}C NMR ($CDCl_3$, ^{1}H decoupled) δ (Me_4Si) 18.12, 35.52, 40.72, 46.89, 103.19, 141.05, 217.62; IR ($CHCl_3$) 1743, 1685, 1621, 1268 cm^{-1}; exact mass calcd for $C_9H_{10}O_2$ m/e 150.068, found 150.069.

Preparation of Oxepin Oxide 10b (n = 2). Azo diepoxide **9b** was prepared by a route analogous to that detailed in the microfilm supplement[20] for homologue **9a**. The azo diepoxide (**9b**) so produced is more thermally stable than **9a** and could be more fully characterized: mp 73–75 °C dec; ^{1}H NMR ($CDCl_3$) δ (Me_4Si) 1.24 (m, 4 H), 1.88 (m, 4 H), 3.34 (AA′XX′, 2 H), 5.75 (AA′,XX′, 2 H); IR (KBr) 2932, 1441, 1209 cm^{-1}; exact mass calcd for $C_{10}H_{12}O_2$ ($M^+ - N_2$) m/e 164.084, found 164.084. Nitrogen extrusion from **9b** in $CDCl_3$ solution at ambient temperature for several hours produced transoid oxepin oxide **10b** quantitatively (^{1}H NMR). Alternatively, sublimation (80 °C, 0.2 mmHg) of solid **9b** (0.216 g, 1.32 mmol) yielded white, crystalline **10b** (0.166 g, 90%); mp 62 °C; ^{1}H NMR ($CDCl_3$) δ (Me_4Si) 1.71 (br m, 4 H), 2.24 (br m, 4 H), 3.60 (AA′XX′, 2 H), 5.03 (AA′XX′, 2 H); ^{13}C NMR ($CDCl_3$) δ (Me_4Si) 25.44 (t, J = 129 Hz), 32.51 (t, J = 130 Hz), 53.36 (d, J = 177 Hz), 108.82 (d, J = 162 Hz), 167.14 (s); IR (CCl_4) 2918, 1689, 1672 cm^{-1}; UV (EtOH) λ_{max} 216 nm (ϵ 7.4 × 10^2); exact mass calcd for $C_{10}H_{12}O_2$ m/e 164.084, found 164.083.

Pyrolyses and Acid-Catalyzed Rearrangements of Transoid Oxepin Oxides 10a,b. Oxepin oxide **10a** was recovered as the sole volatile component after sublimation in a nitrogen stream (7 cm^3 min^{-1}) through a hot tube at 220 and 320 °C (estimated average residence time 40 s). Heating of **10a** at 142 °C in $Cl_2CDCDCl_2$ solution for 2 h caused no perceptible change of the ^{1}H NMR spectrum; at 192 °C extensive decomposition to unidentified products was observed after 1 h. Sublimation of **10a** (0.027 g, 0.18 mmol) in vacuo (60 °C, 0.1 mmHg) through a Pyrex tube, packed with Pyrex beads and heated to 250 °C, gave a mixture of materials including **10a** and *p*-quinol **13a**. Sublimation (60 °C, 0.1 mmHg) of the product mixture gave an oily solid (23 mg) which, by ^{1}H NMR analysis (vs. an internal standard), contained starting **10a** (13 mg, 48% recovered), trace *p*-quinol **13a**, plus unidentified impurites. The oily pot residue (1.1 mg, 8% based on consumed **10a**) was shown to be **13a** by comparison with published spectral data.[22]

Heating of homologue **10b** in $Cl_2CDCDCl_2$ solution at 130–134 °C led within minutes to the appearance of ^{1}H NMR absorptions due to *p*-quinol **13b**. Decomposition of **10b** was virtually complete within 0.5 h giving a mixture of materials with **13b** as a major component (^{1}H NMR). Sublimation of **10b** (0.0415 g, 0.253 mmol) in vacuo (60 °C, 0.1 mmHg) through a Pyrex tube, packed with Pyrex beads and heated to 250 °C, gave a mixture of materials including **10b** and *p*-quinol **13b**. Sublimation (60 °C, 0.1 mmHg) of the product mixture gave an oily solid (30 mg) which by ^{1}H NMR analysis (vs. an internal standard) contained starting **10b** (12 mg, 28% recovered), trace *p*-quinol **13b**, plus unidentified impurities. The crystalline pot residue (12.8 mg, 43% based on consumed **10b**) was shown to be **13b** by comparison with an authentic sample prepared by a literature procedure.[22]

Treatment of the lowest homologue **10a** (0.0122 g, 0.0813 mmol) in $CDCl_3$ solution (ca. 0.5 mL) with a 2% suspension of $MeSO_3H$ in $CDCl_3$ (10 μL) produced no change in the ^{1}H NMR spectrum of **10a** after 5 min at probe temperature (ca. 35 °C). Addition of a second portion of acid (20 μL of 2% suspension) and storage of the sample at ambient temperature for 24 h gave a mixture showing (^{1}H NMR) a predominance of starting material **10a** and easily discernible absorptions due to *p*-quinol **13a**.

Treatment of the homologue **10b** (0.0156 g, 0.0951 mmol) in $CDCl_3$ solution (ca. 0.5 mL) with a 2% suspension of $MeSO_3H$ in $CDCl_3$ (10 μL) induced quantitative rearrangement (^{1}H NMR) to *p*-quinol **13b** within 5 min at probe temperature (ca. 35 °C).

Generation of Oxepin Oxides 10c ⇌ 14c (n = 3). Cope Rearrangement to 15c. Axo diepoxide **9c** prepared as detailed for **9a**[20] displayed mp 89–90 °C dec; ^{1}H NMR ($CDCl_3$) δ (Me_4Si) 1.62 (m, 6 H), 2.08 (m, 4 H), 3.38 (AA′XX′, 2 H), 5.60 (AA′XX′, 2 H); IR (KBr) 2940, 1445, 1211 cm^{-1}; exact mass calcd for $C_{11}H_{14}O_2$ ($M^+ - N_2$) m/e 178.099, found 178.099. Nitrogen extrusion from **9c** in pyridine-d_5 ($t_{1/2}$ ca. 2 days at ambient temperature and ca. 1 h at 60 °C) produces the Cope rearrangement product, oxepin oxide **15c**, quantitatively (^{1}H NMR). Data for **15c**: ^{1}H NMR (py-d_5) δ (Me_4Si) 1.68 (m, 10 H), 4.91 (d, J = 7 Hz, 2 H), 6.28 (d, J = 7 Hz, 2 H); IR (py-d_5) 1675, 1656 cm^{-1}.

Nitrogen extrusion from **9c** in $CDCl_3$ produces spiro ketone **16c** with only traces of acid-labile, intermediate oxepin oxide **15c** visible (^{1}H NMR) during the extrusion process. Spiro ketone **16c** was also produced upon partitioning a pyridine-d_5 solution of oxepin oxide **15c** between $CDCl_3$ and 5% (w/v) aqueous HCl. Data for **16c**: ^{1}H NMR ($CDCl_3$) δ (Me_4Si) 1.57 (m, 8 H), 2.53 (m, 2 H), 4.81 (AA′XX′, 2 H), 6.43 (AA′XX′, 2 H); IR ($CHCl_3$) 2930, 1699, 1679, 1619 cm^{-1}; exact mass calcd for $C_{11}H_{14}O_2$ m/e 178.099, found 178.100.

Nitrogen extrusion from azo diepoxide **9c** (4 mg, 0.019 mmol) at 68 °C ($t_{1/2}$ ca. 20 min) in $CDCl_3$ solution (ca. 0.5 mL) in the presence of trace acid (10 μL of a 2% suspension of $MeSO_3H$ in $CDCl_3$) led to the trapping of **10c** and/or **14c**. Under these conditions aldehyde **19** and spiro ketone **16c** were formed in a ratio of 1:1 (ratio determined

by ^{1}H NMR was constant throughout the nitrogen extrusion process) ^{1}H NMR data for **19**: ($CDCl_3$) δ (Me_4Si) 1.96 (br m, 10 H), 3.45 (d of t, J = 4 and 7 Hz, 1 H), 5.05 (d, J = 7 Hz, 2 H), 9.14 (d, J = 4 Hz, 1 H); ^{1}H decoupling, irradiation at δ 3.45 gives 1.96 (br m, 10 H), 5.05 (s, 2 H), 9.14 (s, 1H); irradiation at δ 5.05 gives 1.96 (br m, 10 H), 3.45 (d, J = 4 Hz, 1 H), 9.14 (d, J = 4 Hz, 1 H); irradiation at δ 9.14 gives 1.96 (br m, 10 H), 3.45 (t, J = 7 Hz, 1 H), 5.05 (d, J = 7 Hz, 2 H). The IR ($CDCl_3$) of the mixture of **16c** and **19** showed 2738 cm^{-1} and a broad carbonyl band, 1700–1725 cm^{-1}. Attempted purification of aldehyde **19** was thwarted by its instability.

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Supplementary Material Available: Procedures for the preparation of several materials (as indicated above) (4 pages). Ordering information is given on any current masthead page.

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(11) A similar effect is seen with 2,7-dimethyloxepin and two related, interconverting oxepin oxides; see ref 5.
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(13) For the parent, *sym*-oxepin oxide, the rate of Cope rearrangement is not quite rapid enough to produce fluxional NMR behavior; see ref 3 and 4.
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Quantitative Prediction of Structure–Reactivity Relationships for Unimolecular Reactions of Unsaturated Hydrocarbons. Development of a Semiempirical Model

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Abstract: A simple theoretical model that has previously been used to make qualitative predictions about substituent and benzannelation effects on the rates of thermal pericyclic reactions has now been shown to give quantitative results for a variety of unsaturated hydrocarbon reactions. These reactions inelude pericyclic and biradical transformations as well as simple homolytic fission to discrete radicals. Substituent effects on the rates of the pericyclic and biradical reactions can be predicted with an uncertainty (least-squares standard deviation) of ±1.7 kcal/mol, while for homolytic fissions the uncertainty is ±4.4 kcal/mol. Possible contributors to the success of the model are discussed. Applications of the model to the Cope rearrangement, Dewar benzene ring opening, and bicyclo[3.2.0]hept-6-ene ring opening are also considered.

A procedure based on simple Hückel molecular orbital (HMO) theory has recently been shown to provide some insight into the qualitative effects of substituents[1] and of benzannelation[2] on the rates of pericyclic reactions. We now report that the same approach provides a quantitative description of these structure-reactivity relationships if one considers only unsaturated hydrocarbon reactants. In addition, the model is found to be applicable to a number of radical and biradical reactions.

The technique involves selection of appropriate models for the reactant and transition state, and then evaluation of the Hückel π-electron energy (E_π) for each. If ΔE_π is defined as the difference in π-electron energy between the model transition state and reactant, the quantity $\Delta\Delta E_\pi$ is then the difference in ΔE_π for two reactions whose rates (or, more specifically, activation enthalpies) are to be compared. In the case of cyclobutene ring openings, it has been noted previously[2] that there is an apparent linear relationship between $\Delta\Delta E_\pi$ and $\Delta\Delta H^\ddagger$, the change in observed activation enthalpy that occurs upon replacement of the cyclobutene double bond by an annelated benzene ring or a pair of exocyclic methylene groups. Since the original investigation covered only four sets of reactions, it was not clear whether this relationship was fortuitous or genuine. The present work extends the investigation to 24 examples of widely varying hydrocarbon reactions and results in a linear $\Delta\Delta E_\pi/\Delta\Delta H^\ddagger$ relationship covering a range of >50 kcal/mol in $\Delta\Delta H^\ddagger$.

The data are classified by reaction type and will be discussed in separate sections. Since the experimental data are drawn from many different sources, some reporting activation energy

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