on 111 mg of unreacted **6b**). Compound **7b**: white crystalline solid; mp 108.5–111 °C; ^{1}H NMR (400 MHz) δ 7.69 (d, 2 H, J = 8.2), 7.30 (d, 2 H, J = 8.0), 6.69 (d, 1 H, J = 8.8), 6.53 (d, 1 H, J = 2.8), 6.48 (dd, 1 H, J_1 = 8.8, J_2 = 2.8), 5.83 (s, OH, broad), 3.83 (s, 3 H), 2.43 (s, 3 H). Anal. Calcd for $C_{14}H_{14}O_5S$: C, 57.1; H, 4.8. Found: C, 57.4; H, 4.9.

2-Hydroxy-5-(tosyloxy)anisole (7c) and 5-Hydroxy-2-(tosyloxy)anisole (8c).[21] Starting material was **6c** (530 mg, 1.18 mmol); $E^1_{1/4} \sim -1.25$ V. From the resulting crude oil was isolated small amounts of **7c** and **8c** in a ratio of 23/77 with significant decomposition. Compound **7c**: ^{1}H NMR (400 MHz) δ 7.74 (d, 2 H, J = 8.4), 7.29 (d, 2 H, J = 8.1), 6.98 (d, 1 H, J = 8.6), 6.33 (d, 1 H, J = 2.8), 6.29 (dd, 1 H, J_1 = 8.6, J_2 = 2.8), 4.90 (s, OH, broad), 3.49 (s, 3 H), 2.44 (s, 3 H). Compound **8c**: ^{1}H NMR (400 MHz) δ 7.70 (d, 2 H, J = 8.2), 7.31 (d, 2 H, J = 8.1), 6.73 (d, 1 H, J = 8.7), 6.61 (d, 1 H, J = 2.6), 6.33 (dd, 1 H, J_1 = 8.7, J_2 = 2.6), 5.50 (s, OH, broad), 3.80 (s, 3 H), 2.45 (s, 3 H).

3-Hydroxy-4-(tosyloxy)anisole (7d) and 4-Hydroxy-3-(tosyloxy)anisole (8d). Starting material was **6d** (250 mg, 0.557 mmol); $E^2_{1/4} \sim -1.15$ V. The crude oil obtained was identified as compound **7d**; compound **8d** was not found. Purification by LPC gave pure **7d** as a light yellow oil (129 mg, 82%). An estimated 11 mg of unreacted **6d** was extrapolated from the NMR of the crude product (96% conversion): ^{1}H NMR (500 MHz) δ 7.74 (d, 2 H, J = 8.4), 7.33 (d, 2 H, J = 8.4), 6.62 (d, 1 H, J = 9.0), 6.53 (d, 1 H, J = 3.0), 6.27 (dd, 1 H, J_1 = 9.0, J_2 = 3.0), 6.06 (s, OH, broad), 3.74 (s, 3 H), 2.46 (s, 3 H). Anal. Calcd for $C_{14}H_{14}O_5S$: C, 57.1; H, 4.8. Found: C, 56.9; H, 4.8.

Methylation. General Procedure. To a 10-mL flask equipped with a stir bar and N_2 balloon was added the phenolic starting material (75–150 g) in CH_3CN (6 mL). To this solution was added t-BuOK (110 mol %). The deep red solution was allowed to stir for 15 min, and then MeI (1000 mol %) was added. A precipitate immediately developed. The reaction was stirred at room temperature under N_2 for 1 day and then poured into a 60-mL solution of 0.5 M KOH and EtOAc, 1/1. The aqueous layer was separated and extracted with EtOAc (1 × 30 mL). The combined organic layers were washed with brine (20 mL), dried, and evaporated, and the crude product was purified by prep plate TLC (hexanes/EtOAc, 2/1).

Methyl 4-Methoxy-3-(tosyloxy)benzoate (13). Starting materials were **4d** (78 mg, 0.24 mmol), t-BuOK (34 mg, 0.30 mmol, 125 mol %), and MeI (155 μL, 2.5 mmol, 1030 mol %). The white powder obtained was **13**: mp 91–92.5 °C; ^{1}H NMR (500 MHz) δ 7.92 (dd, 1 H, J_1 = 8.7, J_2 = 2.1), 7.81 (d, 1 H, J = 2.1), 7.75 (d, 2 H, J = 8.3), 7.31 (d, 2 H, J = 8.2), 6.87 (d, 1 H, J = 8.7), 3.88 (s, 3 H), 3.63 (s, 3 H), 2.45 (s, 3 H). Anal. Calcd for $C_{16}H_{16}O_6S$: C, 57.1; H, 4.8. Found: C, 57.0; H, 4.5.

2-Methoxy-4-(tosyloxy)anisole (14). Starting materials were **7b** (152 mg, 0.516 mmol), t-BuOK (60 mg, 0.535 mmol, 104 mol %), and MeI (1000 μL, 16.1 mmol, 3110 mol %). The light yellow oil obtained was **14**: ^{1}H NMR (500 MHz) δ 7.70 (d, 2 H, J = 8.3), 7.31 (d, 2 H, J = 8.3), 6.70 (d, 1 H, J = 8.7), 6.51 (d, 1 H, J = 2.7), 6.48 (dd, 1 H, J_1 = 8.7, J_2 = 2.7), 3.84 (s, 3 H), 3.74 (s, 3 H), 2.45 (s, 3 H). Anal. Calcd for $C_{15}H_{16}O_5S$: C, 58.4; H, 5.2. Found: C, 58.4; H, 5.3.

3-Methoxy-4-(tosyloxy)anisole (15). Starting materials were **7d** (156 mg, 0.530 mmol), t-BuOK (66 mg, 0.588 mmol, 111 mol %), and MeI (500 μL, 2.5 mmol, 1520 mol %). The light yellow solid obtained was **15**: mp 89–91.5 °C; ^{1}H NMR (500 MHz) δ 7.71 (d, 2 H, J = 8.3), 7.27 (d, 2 H, J = 8.3), 7.03 (d, 1 H, J = 9.0), 6.34–6.37 (m, 2 H, AB), 3.75 (s, 3 H), 3.48 (s, 3 H), 2.42 (s, 3 H). Anal. Calcd for $C_{15}H_{16}O_5S$: C, 58.4; H, 5.2. Found: C, 58.6; H, 5.2.

Registry No. **1a**, 2411-83-8; **1b**, 2150-47-2; **1c**, 2150-46-1; **1d**, 2150-43-8; **2a**, 137668-91-8; **2b**, 137668-92-9; **2c**, 137668-93-0; **2d**, 137668-94-1; **3a**, 137668-95-2; **3b**, 137668-96-3; **3c**, 94033-94-0; **4a**, 137668-97-4; **4b**, 137668-98-5; **4d**, 137668-99-6; **5a**, 934-00-9; **5b**, 6100-60-3; **5c**, 824-46-4; **5d**, 3934-97-2; **6a**, 137669-00-2; **6b**, 137669-01-3; **6c**, 137669-02-4; **6d**, 137669-03-5; **7a**, 137669-04-6; **7b**, 137669-05-7; **7c**, 137669-06-8; **7d**, 137669-07-9; **8a**, 137669-08-0; **8b**, 137669-09-1; **8c**, 137669-10-4; **9**, 137669-11-5; **10**, 51207-44-4; **11**, 137669-12-6; **12**, 4416-67-5; **13**, 137669-13-7; **14**, 137669-14-8; **15**, 137669-15-9; 5-chloro-1-phenyltetrazole, 14210-25-4.

Supplementary Material Available: ^{1}H NMR spectra for compounds **10** and **12**, cyclic voltammograms for compounds **2a–d** and **6a–d**, and NOESY spectra for compounds **13–15** (13 pages). Ordering information is given on any current masthead page.

(21) Phenols **7c** and **8c** were characterized fully as their corresponding methyl ethers **14** and **15**, respectively.

Radical Reactions of Epoxides. Chlorine Atom Abstraction from α- and β-Chloro Epoxides by the Triphenyltin Radical[1]

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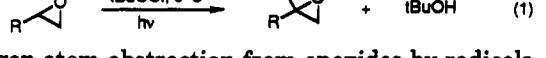
The four isomers of chloroepoxypropane have been prepared, and their relative reactivities with triphenyltin hydride have been determined. The three α-chloroepoxypropanes react at a much slower rate than does epichlorohydrin, the only β-chloro epoxide of the four. The nature of the increased reactivity for the β-chloro epoxides has been investigated by studying two pair of diastereomeric β-chloro epoxides, and a single acyclic β-chloro ether. The results are discussed in terms of the inductive, resonance, and stereoelectronic effects of the epoxide.

Introduction

The first studies of the free-radical chemistry of epoxides in solution were reported by Walling and co-workers in 1962.[2] They found that the photoinitiated reactions of epoxides with *tert*-butyl hypochlorite formed α-chloro epoxides as the major products (eq 1). Subsequent studies



(1)

of hydrogen atom abstraction from epoxides by radicals including bromine atom,[3] chlorine atom,[4] and *tert*-butoxyl radical[5] have appeared. In nearly every case, abstraction of an α-hydrogen atom from the epoxide can account for

(1) Initial presentation of results at the 201st National Meeting of the American Chemical Society, Atlanta, GA, April 16, 1991.

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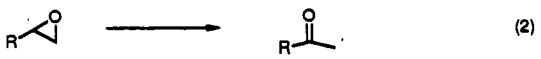
0022-3263/92/1957-0840$03.00/0

all of the observed products. Sabatino and Gritter have also reported small amounts of products derived from β-hydrogen atom abstraction in the reactions of epoxides with *tert*-butoxyl radicals at high temperatures (150 °C).[6] One other group has reported products from the reactions of epoxides with *N*-bromosuccinimide (NBS) which are apparently formed via exclusive β-hydrogen atom abstraction;[7] however, these results should possibly be regarded with caution.

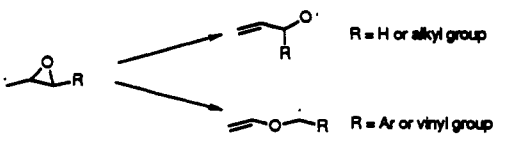
In the intervening 30 years several methods, apart from hydrogen atom abstraction, have been employed in order to generate epoxide radicals either at a carbon atom in the epoxide ring (α-epoxy radicals) or at an exocyclic position (β-epoxy radicals). The methods used to generate α-epoxy radicals include decarbonylation of an α,β-epoxyacyl radical[8] and chlorine atom abstraction from α-chloro epoxides by trialkyltin radicals.[9] β-Epoxy radicals have been generated by homolytic decomposition of certain thioimidizoles,[10] Norrish type I cleavage of β,γ-epoxy ketones,[11] trialkyltin hydride reduction of α,β-epoxy ketones,[12] and bromine atom abstraction from a β-bromo epoxide by a trialkyltin radical.[13]

Rearrangements have been observed for both types of epoxy radicals. In the case of α-epoxy radicals, ESR experiments have demonstrated the ring-opening rearrangement to α-carbonyl radicals (eq 2).[14] This rearrangement has also been studied using molecular orbital calculations.[15] Ring-opening rearrangement of β-epoxy radicals is analogous to the well studied rearrangement of cyclopropylcarbinyl radicals.[16] Ring-opening occurs via carbon–oxygen bond cleavage except in cases where carbon–carbon bond cleavage generates an allylic or a benzylic radical (Scheme I).[17] No example of spectroscopic observation or chemical trapping of a β-epoxy radical prior to ring-opening rearrangement has been reported.


(2)

In order to compare ease of generation of α- and β-epoxy radicals directly, we desired an approach which could be used to form radicals in a regiospecific manner. Halogen atom abstraction from a series of halogenated epoxides by trialkyltin radicals provides a regiospecific method for the generation of epoxy radicals. We herein report the relative reactivities of a series of β- and α-chloropropylene oxides (**1–4**) with triphenyltin hydride. We have also investigated the possibility of stereoelectronic effects in the reduction of two pairs of diastereomeric β-chloro epoxides (**5**, **6** and **7**, **8**).

Scheme I



Scheme II

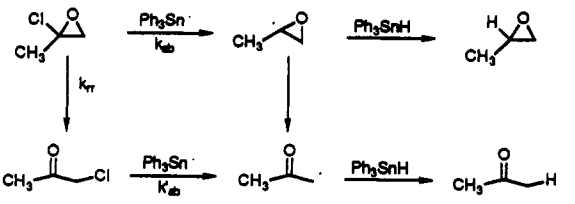


Table I. Reactions of Alkyl Chlorides with Triphenyltin Hydride at 70 °C[a]

substrate	no. of runs	k_{rel} (vs cyclohexyl chloride)
cis-1-chloro-1,2-epoxypropane (**4**)[b]	3	0.032 ± 0.01
trans-1-chloro-1,2-epoxypropane (**3**)[b]	3	0.036 ± 0.01
2-chloro-1,2-epoxypropane (**2**)[b]	3	0.11 ● 0.01
neophyl chloride	5	0.32 ± 0.03
1-chloro-2-methoxyethane	6	0.40 ± 0.02
cyclohexyl chloride	–	(1)
epichlorohydrin (**1**)	4	2.00 ± 0.02
erythro-3-chloro-1,2-epoxybutane (**5**)	5	5.19 ● 0.14
threo-3-chloro-1,2-epoxybutane (**6**)	5	5.78 ● 0.23
trans-2-chloro-7-oxabicyclo[4.1.0]heptane (**7**)	5	5.45 ± 0.30
cis-2-chloro-7-oxabicyclo[4.1.0]heptane (**8**)	5	11.1 ± 1.2
benzyl chloride	5	22.3 ± 1.9

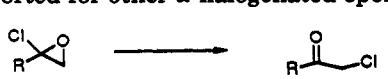
[a] Competitive reactions run at 70 °C and followed by disappearance of starting material (NMR or GC). [b] Relative rates represent an upper limit on the reactivity for the ring-chlorinated epoxides due to competitive rearrangement to the α-chloro carbonyl compounds followed by reduction, see text.

Results

Walling's chlorination of propylene oxide using *tert*-butyl hypochlorite[1a](eq 1) was repeated in order to form 2-chloropropylene oxide (**2**). The reaction produced one major product (75%) and two minor products (15 and 10%) when carried out at 0 °C. Isolation and identification showed the products to be 2-chloro-1,2-epoxypropane (**2**), *trans*-1-chloro-1,2-epoxypropane (**3**), and *cis*-1-chloro-1,2-epoxypropane (**4**), respectively. It proved more effective to prepare **3** and **4** by shaking a benzene solution of 1,1-dichloro-2-propanol with aqueous sodium hydroxide.[18]

Each of the α-chloro epoxides was characterized by NMR spectroscopy as described in the experimental section.

Rearrangement of the α-chloro epoxides to form α-chloro carbonyl compounds was observed under even the mildest of conditions. For example, 20–30% of compound **2** underwent isomerization to chloroacetone when stored in the refrigerator for 2 days. Rearrangements of this type have been reported for other α-halogenated epoxides (eq 3).[19]


(3)

(6) Sabatino, E. C.; Gritter, R. J. *J. Org. Chem.* **1963**, *28*, 3437.
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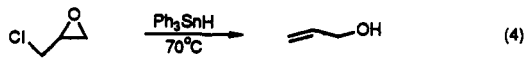
The relative rates of reaction which appear in Table I represent the results of direct competition for a pair of chlorides reacting with a limiting amount of triphenyltin hydride at 70 °C, as determined by disappearance of starting materials. The reference compound was either neophyl chloride or cyclohexyl chloride (depending on reactivity). Replicate reactions were run to approximately 10–15% completion of the less reactive substrate. The reactions were analyzed by 300-MHz NMR spectrometer or by capillary GC.

The study of kinetics for the α-chloro epoxides was complicated by the tendency of these compounds to rearrange. Photoinitiated reaction of 2 with triphenyltin hydride in benzene gave acetone as the major product. There was no propylene oxide observed among the reaction products. Scheme II shows the possible routes to acetone. Similarly, the reaction of 3 and 4 under identical conditions gave no sign of propylene oxide as a product. For these compounds a number of new signals were observed in the NMR analysis. Although we were unable to determine the structures for all of the products, the presence of propionaldehyde and the absence of propylene oxide were confirmed. Independent determination of a relative rate of reduction for chloroacetone indicates that k'_{ab} (Scheme II) is much greater than the overall rate of reduction for the disappearance of 2. On the basis of this result, we have assigned the measured rates of disappearance for compounds 2–4 as upper limits for the rates of chlorine atom abstraction from the α-chloro epoxides, realizing that they actually may represent the sum of rates for the chlorine atom abstraction (k_{ab}) and starting material rearrangement (k_{rr}).

In contrast to the complicated picture which was observed for the α-chloro epoxides, epichlorohydrin (1), the simplest β-chloro epoxide, reacted with triphenyltin hydride to give only allyl alcohol (eq 4). The relative rate



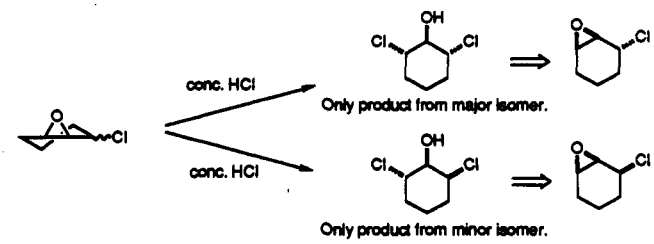
(4)

for the reduction of 1 was determined as above and is reported in Table I.

We have also studied the triphenyltin hydride reductions of *erythro*- and *threo*-2-chloro-3,4-epoxybutane (5 and 6) and *trans*- and *cis*-2-chloro-7-oxabicyclo[4.1.0]heptane (7 and 8). These compounds were prepared by epoxidation of the corresponding allylic chlorides using *m*-CPBA.[20] In both cases, separation of diastereomers was accomplished by preparative GC. Identification of 5 and 6 was based on comparison of ^{1}H NMR chemical shifts with published values.[21] Identification of 7 and 8 was not possible using ^{1}H or ^{13}C NMR techniques. However, treatment of either isomer with concentrated hydrochloric acid formed a single HCl adduct via anti epoxide ring opening.[22] The structures of the HCl adducts were easily assignable by NMR spectroscopy and allowed for a structural identification of these chloro epoxides (Scheme III).

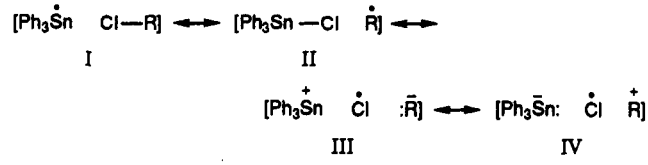
The reductions of these β-chloro epoxides using triphenyltin hydride afforded exclusively the corresponding allylic alcohols with excellent material balances. Relative rates for these compounds are also included in Table I.

Scheme III



Discussion

The reaction of trialkyltin hydrides with organic chlorides has been extensively studied.[13a,23,24] The rate-limiting step is chlorine atom abstraction by the trialkyltin radical. The transition state for this atom abstraction can be represented by a hybrid of the canonical forms I–IV.



The electropositive nature of tin would indicate a greater participation by form III which translates into negative charge buildup at the chlorine-bearing carbon during the reaction. It is well established that substrates which can stabilize negative charge at the chlorine-bearing carbon show faster rates of reaction with trialkyltin radicals.[13a,23,24] For the present series of compounds, a model which involves negative charge buildup in the transition state would predict an unfavorable interaction when the chlorine-bearing carbon atom is directly attached to an oxygen atom, as is the case for the α-chloro epoxides. Conversely, an epoxide ring attached to the chlorine bearing carbon (i.e., β-chloro epoxides) would be expected to stabilize negative charge development in the transition state. It has been shown that the σ value for a *p*-oxiranyl substituent is positive.[25]

For the isomeric chloropropylene oxides 1–4, the order of reactivity is $1 \gg 2 > 3 \approx 4$. This same order of reactivity is predicted by semiempirical molecular orbital calculations based upon energy differences between the starting chloro epoxides and the corresponding isomeric anions at the AM1 level of theory.[26] The logarithms of the relative rates for the isomeric chloroepoxypropanes correlate well with these calculated energy differences ($r = 0.99$). Calculated energy differences for the analogous radicals or radical anions did not demonstrate comparably good correlations ($r = 0.75$ and 0.71, respectively).

The rate of reaction for epichlorohydrin, the least reactive β-chloro epoxide studied, was six times faster than

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(27) QCPE program no. 506.

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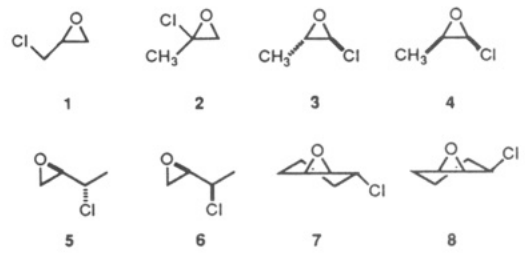

Figure 1. Alternatives for negative-charge stabilization by the epoxide in the transition state of chlorine atom abstraction.

that for neophyl chloride and twice as fast as that observed for cyclohexyl chloride, a more favored secondary alkyl chloride. These relative reactivities are contrary to the generally observed trend for halogen atom abstractions by tin radicals in which tertiary chlorides react faster than secondary chlorides which in turn react faster than primary chlorides.[13a]

It is apparent that the epoxide has an accelerating effect on the rate of chlorine atom abstraction from a neighboring carbon. Can the nature of this accelerating effect be addressed?

The rate-accelerating effect of the β-epoxy substituent can be due to inductive stabilization of negative charge buildup in the transition state (Figure 1a), conjugative stabilization of negative charge buildup in the transition state by the epoxide ring (Figure 1b), or a combination of both effects. The importance of inductive stabilization can be addressed by comparing the reactivity of β-chloro epoxides with acyclic β-chloro ethers.[29] For example, epichlorohydrin is five times more reactive than 1-chloro-2-methoxyethane (Table I). This suggests that conjugation is important in the stabilization of negative charge development in the transition state. However, while the β-chloro epoxides react faster than alkyl chlorides and acyclic β-chloro ethers, the effect of the epoxide is far less than the effect of a phenyl group as seen by comparing the reactivities for epichlorohydrin and benzyl chloride (Table I). Nonetheless, orbital overlap (conjugation) involving the epoxide appears to be important in the transition state, and an optimum dihedral angle between the chlorine–carbon bond and the carbon–oxygen bond should exist. Calculations by Dannen[30] predict that there is an optimum angle between the developing negative charge and the carbon–oxygen bond of the epoxide. This will give rise to a stereoelectronic attenuation of the overlap which should be reflected as rate differences among compounds with fixed dihedral angles.

Agosta and co-workers failed to observe stereoelectronic effects in the photochemical cleavage of two diastereomeric β,γ-ketones.[11c] They suggested that participation of zwitterionic resonance contributors to the intermediate biradical may complicate the study of stereoelectronic

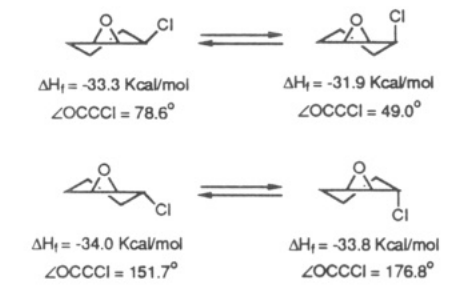

Figure 2. Summary of AM1 calculations for the isomeric 2-chloro-7-oxabicyclo[4.1.0]heptanes.

effects in the intramolecular radical ring opening of epoxides.

The two pair of diastereomeric β-chloroepoxides which we have studied should demonstrate whether any stereoelectronic effect might exist. For the open-chain compounds **5** and **6**, we have observed only a small difference in reactivity (5–10%) of the threo and erythro isomers despite the variation in conformational stability for any given dihedral angle. Both compounds were more than five times as reactive as chlorocyclohexane.

trans-2-Chloro-7-oxabicyclo[4.1.0]heptane (**7**) showed a reactivity comparable to the other secondary β-chloro epoxides. However, a 2-fold increase in reactivity was observed for the cis isomer **8**. These bicyclic compounds have a restricted range for the dihedral angles. Compound **7** has a chlorine–carbon–carbon–oxygen bond angle of either 152 or 177° depending on conformation while the angle for compound **8** is either 49 or 79°, based on structure minimization calculations at the AM1 level of theory (Figure 2). The calculated energies for the isomeric trans and cis compounds show that the cis compound has a higher energy by 0.7 kcal/mol. While the dramatic rate increase for the cis compound may appear to support a stereoelectronic effect, the difference in energies of the starting β-chloro epoxides is of the correct magnitude to explain the rate acceleration on the basis of strain relief alone. Thus, the relative rates of reaction for the β-chloro epoxides do not provide definitive evidence for a stereoelectronic attenuation of the conjugative effect of epoxides.

Conclusions

The rates of chlorine atom abstraction from isomeric chloro epoxides by triphenyltin radicals follow the expected trend based on a model involving negative charge development in the transition state. α-Chloro epoxides react at a much slower rate than do β-chloro epoxides with triphenyltin radicals. The β-chloro epoxides are more reactive than alkyl chlorides, apparently due to both inductive and conjugative effects of the epoxide. Attempts to observe a dependence of relative rate on the geometry of the chloro epoxide gave ambiguous results.

Experimental Section

All reagents were purified using standard methods.[31] Of the compounds studied, epichlorohydrin, 1-chloro-2-methoxyethane, benzyl chloride, cyclohexyl chloride, and neophyl chloride were obtained commercially. The remaining compounds were prepared as follows.

Preparation of α-Chloro Epoxides. Freshly prepared *tert*-butyl hypochlorite[32] was used in the photochlorination of propylene oxide. A mixture of propylene oxide and *tert*-butyl

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hypochlorite in a ratio of 3:1 was irradiated at 0 °C until the yellow color had disappeared and then for an additional 0.5 h. Preparative GC was used to collect the three new products. The major product (75%) was identified as 2-chloro-1,2-epoxypropane (2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.10 (1 H, d, J = 4.9 Hz), 2.83 (1 H, d, J = 4.9 Hz), 1.89 (3 H, s, CH_3). The other products (15 and 10%) were identified as *trans*- and *cis*-1-chloro-1,2-epoxypropane (3 and 4), respectively. ^{1}H NMR (3) (300 MHz, $CDCl_3$): δ 4.82 (1 H, d, J = 1.0 Hz), 3.22 (1 H, dq, J = 1.0 and 5.2 Hz) 1.36 (3 H, d, J = 5.2 Hz). ^{1}H NMR (4) (300 MHz, $CDCl_3$): δ 5.16 (1 H, d, J = 2.8 Hz), 3.18 (1 H, dq, J = 2.8 and 5.4 Hz), 1.49 (3 H, d, J = 5.4 Hz).

Preparation of *erythro*- and *threo*-3-Chloro-1,2-epoxybutane. Epoxidation of 3-chloro-1-butene with *m*-CPBA in refluxing CH_2Cl_2 gave a 1:1 mixture of the erythro and threo compounds 5 and 6. Isolation of each isomer was accomplished by preparative GC. ^{1}H NMR (5) (300 MHz, $CDCl_3$): δ 3.64 (1 H, p, J = 6.7 Hz), 3.08 (1 H, m), 2.88 (1 H, t, J = 4.2 Hz), 2.69 (1 H, dd, J = 4.7 and 2.5 Hz), 1.61 (3 H, d, J = 6.6 Hz). ^{13}C NMR (5) (75.5 MHz, $CDCl_3$): δ 56.8, 55.5, 47.2, 21.8. ^{1}H NMR (6) (300 MHz, $CDCl_3$): δ 3.80 (1 H, p, J = 6.7 Hz), 3.15 (1 H, m), 2.89 (1 H, dd, J = 4.7 and 4.0 Hz), 2.72 (1 H, dd, J = 4.8 and 2.5 Hz), 1.55 (3 H, d, J = 6.7 Hz). ^{13}C NMR (6) (75.5 MHz, $CDCl_3$): δ 57.6, 55.7, 46.4, 20.6.

Preparation of *trans*- and *cis*-2-Chloro-7-oxabicyclo[4.1.0]heptane. Epoxidation of 3-chlorocyclohexene with *m*-CPBA in refluxing CH_2Cl_2 gave a 9:1 mixture of compounds 7 and 8. Separation and isolation of each isomer was accomplished by preparative GC. Treatment of each isomer with an equivalent of concd HCl gave a single isomer of 1,3-dichlorocyclohexan-2-ol (see text). ^{1}H NMR (7) (300 MHz, $CDCl_3$): δ 4.35 (1 H, t, J = 4.8 Hz), 3.29 (1 H, d, J = 4.2 Hz), 3.25 (1 H, t, J = 3.4 Hz), 1.96 (3 H, m), 1.60 (2 H, m), 1.32 (1 H, m). ^{13}C NMR (7) (75.5 MHz, $CDCl_3$): δ 55.0, 54.9, 52.2, 28.8, 23.1, 15.1. HRMS: calcd for $^{12}C_6{}^1H_9{}^{16}O_1{}^{35}Cl_1$ 132.03419, found 132.03419, ^{1}H NMR (8) (300 MHz, $CDCl_3$): δ 4.27 (1 H, ddd, J = 10.0, 5.3, and 1.9 Hz), 3.32 (2 H, m), 1.70 (5 H, m), 1.27 (1 H, m). ^{13}C NMR (8) (75.5 MHz, $CDCl_3$): δ 57.4, 56.5, 55.3, 29.4, 22.3, 20.7. HRMS: calcd for $^{12}C_6{}^1H_9{}^{16}O_1{}^{35}Cl_1$ 132.03419, found 132.03419.

Kinetics. All kinetic studies were run in replicate on pairs of substrates. The two substrates, along with Ph_3SnH, an internal standard, and a solvent (benzene or cyclohexane) were mixed in an approximate ratio of 1:1:1:0.5:10. Aliquots were sealed in Pyrex ampules, under a reduced pressure of N_2, after three freeze–thaw cycles. In each case one of the ampules was reserved for analysis of starting material. The reactions were run in a temperature-controlled oil bath at 70 ± 0.5 °C. Reaction times were varied in order to achieve 15–90% reaction of each substrate. Relative rates were determined by disappearance of starting material, as measured by integration of ^{1}H NMR (300 MHz) or capillary GC.

Registry No. 1, 106-89-8; 2, 5950-21-0; 3, 21947-76-2; 4, 21947-75-1; 5, 52066-40-7; 6, 52066-41-8; 7, 137940-88-6; 8, 137940-89-7; 1-chloro-2-methoxyethane, 627-42-9; benzyl chloride, 100-44-7; cyclohexyl chloride, 542-18-7; neophyl chloride, 515-40-2; propylene oxide, 75-56-9; 3-chloro-2-butene, 563-52-0; 3-chlorocyclohexene, 2441-97-6; triphenylstannane, 892-20-6; triphenylstannyl, 17272-58-1.

Isolation and Structure Determination of Pentalenolactones A, B, D, and F

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Four new metabolites related to pentalenolactone have been isolated, pentalenolactone A (17), B (18), D (7), and F (10), and their structures established by a combination of ^{1}H and ^{13}C NMR, ^{1}H NOE, and ^{1}H COSY spectroscopy, assisted by molecular modeling calculations. The structure and stereochemistry of pentalenolactone D phenacyl ester (21) was established by X-ray crystallography. Each of these metabolites may be important intermediates or shunt metabolites in the biosynthesis of pentalenolactone (16).

The sesquiterpene antibiotic pentalenolactone (16), which has been isolated from a variety of *Streptomyces* species, is a rare example of a cyclic terpenoid produced by a prokaryotic organism (Scheme I). Following the original isolation in 1957,[1] the structure and absolute configuration were eventually assigned in 1970 by a combination of spectroscopic and X-ray crystallographic methods.[2,3] In addition to exhibiting a broad spectrum of activity against a wide variety of organisms, including Gram-positive and Gram-negative bacteria, pentalenolactone has been shown to block glycolysis by selective inhibition of glyceraldehyde-3-phosphate dehydrogenase from both prokaryotic (*Escherichia coli, Bacillus subtilis*) as well as eukaryotic sources (yeast, spinach, rabbit muscle).[4] Pentalenolactone has also been reported to exhibit potent and specific antiviral activity.[5] Studies in our own laboratory have shown that pentalenolactone is a time-dependent, irreversible inactivator of glyceraldehyde-3-phosphate dehydrogenase whose inhibitory action is due to specific reaction with all four active-site cysteines of the tetrameric enzyme.[6] Additional studies with model thiols have suggested that the thiol residue is alkylated by ring opening at C-10 of the epoxy lactone moiety although this has yet to be demonstrated directly for inactivation of the enzyme itself.[6b]

We have demonstrated the sesquiterpenoid biosynthetic origin of pentalenolactone[7] and carried out extensive

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