ORGANIC LETTERS

2008
Vol. 10, No. 12
2413−2416

Conformational Effects in Acid-Mediated Ring Opening of Epoxides: A Prominent Role of the Oxirane Walsh Orbital

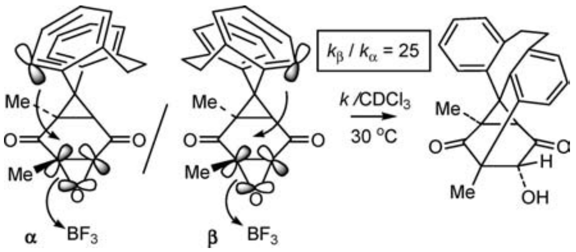
Takumi Oshima,* Haruyasu Asahara, Emi Kubo, Saki Miyamoto, and Kyoko Togaya

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, 2-1, Yamada-oka, Suita, Osaka 565-0871, Japan

oshima@chem.eng.osaka-u.ac.jp

Received March 26, 2008

ABSTRACT



A kinetic study has been made of the BF_3-mediated ring opening of two rigid conformers (α and *β*) of *m*- and *p*-dimethyl-substituted homobenzoquinone epoxides spiro-linked with a twist-boat dibenzocycloheptene ring as compared with the conformationally mobile epoxides bearing diphenyl groups. The rates of the regioselective ring opening were dependent on the topological alignment of the dibenzocycloheptene ring as well as the substitution pattern of the quinone dimethyl groups, indicating *π*-aryl participated orbital interaction with the vacant Walsh orbital of the oxirane ring.

The acid-mediated ring-opening reactions of epoxides have attracted continuous interest from the synthetic and mechanistic viewpoints.[1] These reactions generally proceed through regio- and stereoselective ring cleavage via a S_N2-type anti nucleophilic displacement.[2] These stereochemical features are much affected by the steric environments in the oxirane ring. Despite numerous investigations into the mechanistic aspects, a possible role of the characteristic oxirane Walsh orbital in the anti nucleophilic ring cleavage of epoxides remains to be elucidated.

To clarify such an orbital interaction, we have investigated the neighboring group participation that will affect the reactivity by way of the geometrically controlled through-space electronic interactions with the incipient cation center (or the vacant orbital).[3] In particular, *π*-aryl participation is commonly recognized in the organic reactions of compounds possessing the aromatic nucleus (or nuclei) adjacent to or in the topological neighborhood, promoting reaction via a rate-determining aryl-assisted transition state.[4] In this regard, the conformational effects in the ring opening of an appropriately designed aryl-substituted epoxides will provide very useful insights into the geometrical features of orbital interaction with the oxirane Walsh orbital in the transition state.

In our previous paper, we reported that the reaction of 5-diazo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene with *p*- and *m*-dimethyl-substituted quinones gives the conforma-

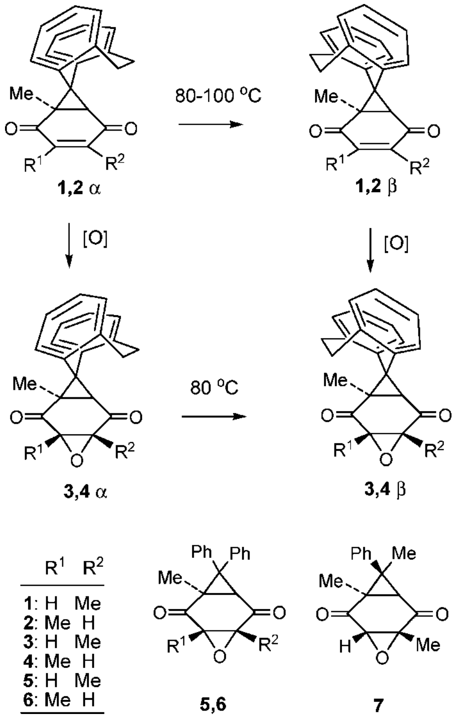
---

(1) (a) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. (b) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 3, p 733. (c) Fujita, H.; Yoshida, Y.; Kita, Y. *Yuki Gosei Kagaku Kyokaishi* **2003**, *61*, 133. (d) Giner, J.-L.; Li, X.; Mullins, J. J. *J. Org. Chem.* **2003**, *68*, 10079.

(2) (a) Posner, G. H.; Rogers, D. Z. *J. Am. Chem. Soc.* **1977**, *99*, 8214. (b) Bellucci, G.; Berti, G.; Ingrosso, G.; Mastrorilli, E. *J. Org. Chem.* **1980**, *45*, 299. (c) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768. (d) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. (e) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001. (f) Brandes, B. D.; Jacobsen, E. N. *Synlett* **2001**, 1013. (g) Schneider, C. *Synthesis* **2006**, 3919. (h) Hirai, A.; Tonooka, T.; Tanino, K.; Miyashita, M. *Chirality* **2003**, *15*, 108.

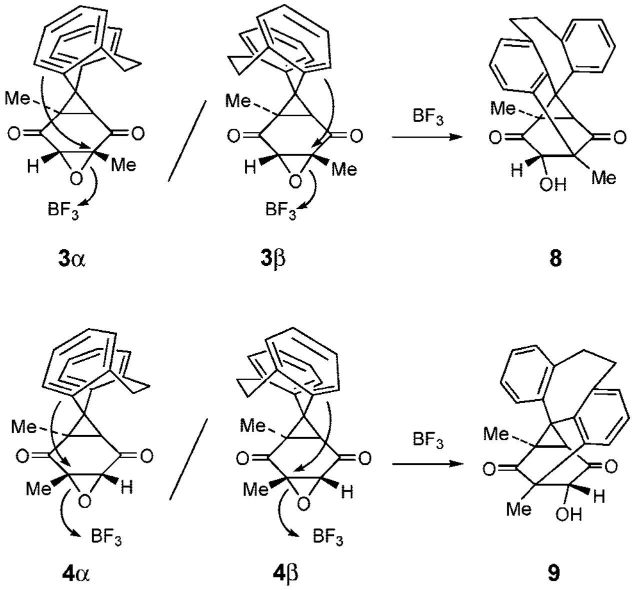
10.1021/ol800535c CCC: $40.75

Scheme 1



tionally less stable spiro-linked homobenzoquinones **1**,**2**α (hereafter called the α-conformer) as shown in Scheme 1.[5] These compounds slowly underwent the conformational inversion of the twist-boat dibenzocycloheptene ring to afford the more stable distinct twist-boat forms **1**,**2***β* (called *β*-conformer) at 80−100 °C (vide infra). Here, we assigned α and *β* for the conformer in which the twist-boat dibenzocycloheptene ring is folded in the opposite and the same side with respect to the cyclopropane Me substituent, respectively. These homobenzoquinones were found to be easily oxidized to the conformationally retained corresponding epoxides **3**,**4**α and **3**,**4***β*, as verified by X-ray crystal analysis.[6]

Scheme 2



As described previously,[6b] BF_3-mediated reaction of these α- and *β*-conformers of epoxides **3** and **4** resulted in the regioselective oxirane ring opening at the Me-substituted C−O bonds. The following intramolecular nucleophilic attack (transannular cyclization) by the *endo*-aromatic nucleus (S_E2-Ar reaction) afforded the identical tricyclic diketoalcohols **8** and **9** as the primary products (Scheme 2). Here, it is noted that the **3**α and **4***β* were subjected to the whole inversion of the twist-boat form in these reactions, as represented by X-ray crystal structure of **8**.[6b] Similar S_E2-Ar reactions were also found for the conformationally mobile related epoxides **5**−**7** to provide the corresponding tricyclic diketo-alcohols via the regioselective ring cleavage followed by a transannular cyclization.[6b] Due to the appreciable thermal stability, the α- and *β*-conformers of epoxides **3** and **4** take advantage of evaluating the conformational effects (i.e., stereoelectronic effects) on the possible anti *π*-aryl participation in the oxirane ring cleavage. Therefore, we have made a kinetic investigation of acid-mediated rearrangement of each conformer of **3** and **4** in comparison with the reference epoxides **5**−**7** (Scheme 1).

First, to assess the conformational stability of the less stable α-conformers of **1**−**4**, we carried out a kinetic study of the nonmediated thermal interconversion into the corresponding *β* isomers by ^{1}H NMR in $CDCl_3$ at 80 °C in a sealed tube. Only the epoxide **3**α established the equilibration ($\alpha:\beta = 4:96$), whereas the other α-conformers were completely transformed into the corresponding *β*-isomers. The first-order rate constants k_1 thus obtained are given in Table 1. The estimated energy barriers from the k_1 values for α → *β* conversion are 117−125 and 108−109 kJ mol^{-1} at 80 °C for **1**,**2** and **3**,**4**, respectively. These values are high enough to prevent the conformational interconversion at ordinary temperature, although the epoxidation slightly reduced the energy barriers by ~17 kJ mol^{-1}. Thus the thermal stability increases in the order of **2**α > **1**α > **3**α > **4**α. The conformational locking for the intrinsically flexible parent dibenzocycloheptene ring[7] can be ascribed to the repulsive van der Waals interaction between (1) the peri-hydrogen atom of *endo*-aromatic ring and the quinone plane as well

---

(3) Isaacs, N. S. *Physical Organic Chemistry*, 2nd ed.; Longman Scientific & Technical: Essex, U.K., 1995; Chaper 13, p 643.

(4) (a) Lancelot, C. J.; Cram, D. J.; Scheyer, P. v. R. *Carbenium Ions*; Olah, G. A., Scheyer, P. v. R., Eds.; Wiley-Interscience: New York, 1972: Vol. 3, Chapter 27, p 1347. (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; Wiley: New York, 2001; Chapter 10, p 407. (c) Peeran, M.; Wilt, J. W.; Subramanian, R.; Crumrine, D. S. *J. Org. Chem.* **1993**, *58*, 202. (d) Kevil, D. N.; D'Souza, M. J. *J. Chem. Soc., Perkin Trans.* **1997**, *2*, 257. (e) Fujio, M.; Goto, N.; Dairokuno, T.; Goto, M.; Saeki, Y.; Okusaka, Y.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3072. (f) Nagumo, S.; Ono, M.; Kakimoto, Y.; Furukawa, T.; Hisano, T.; Mizukami, M.; Kawahara, N.; Akita, H. *J. Org. Chem.* **2002**, *67*, 6618. (g) Río, E. d.; Menéndez, M. I.; López, R.; Sordo, T. L *J. Am. Chem. Soc.* **2001**, *123*, 5064.

(5) Oshima, T.; Fujii, S.; Takatani, T.; Kokubo, K.; Kawamoto, T. *J. Chem. Soc., Perkin Trans.* **1999**, *2*, 1783.

(6) (a) Asahara, H.; Koizumi, T.; Mochizuki, E.; Oshima, T. *Acta Crystallogr., Sect. C* **2006**, *62*, 136. (b) Asahara, H.; Kubo, E.; Togaya, K.; Koizumi, T.; Mochizuki, E.; Oshima., T. *Org. Lett.* **2007**, *9*, 3421.

as (2) the peri-hydrogen atom of *exo*-aromatic ring and the cyclopropane Me substituent.[5]

Keeping this in mind, we next investigated the kinetics of acid-mediated reactions of the α- and *β*-families of the conformationally locked **3** and **4** as well as the mobile **5**−**7**. The representative kinetic run was performed at 30 °C in a NMR tube containing epoxide (6.9 mg) and $BF_3{\cdot}OEt_2$ (28.8 mg, 0.296 M) in $CDCl_3$ (0.65 mL) by following the decay of the diagnostic Me group of the relevant epoxide (TMS as an internal standard) over the second half-lives. During all kinetic runs, no indication of the conformational isomerization α → *β* was found by the NMR measurement, in accordance with the significant thermal stability of these α-conformers. The observed pseudo-first-order rate constants (k_{obs}) were divided by the concentration of the acid to obtain the second-order rate constants k_2. The values of k_2 thus obtained are listed along with the relative rate constants k_2^{rel} (vs the reference **5**) in Table 1.

Table 1. Rate Constants for Conformational Inversion of **1**α and **2**α at 80 °C in $CDCl_3$ and BF_3-Mediated Ring Opening of Epoxides **3**−**4**α,*β* and **5**−**7** at 30 °C in $CDCl_3$

				ring opening of epoxide	
run	compd	R^1, R^2	inversion $10^5 \times k_1$ (s^{-1})	$10^4 \times k_2{}^a$ ($M^{-1}\ s^{-1}$)	$k_2{}^{rel}$
1	**1**α	H, Me	4.05^b		
2	**2**α	Me, H	0.27^b		
3	**3**α	H, Me	59.5^c	6.98	1.4
4	**3***β*	H, Me	2.72^d	1.84	0.4
5	**4**α	Me, H	89.3^b	3.99	0.8
6	**4***β*	Me, H		98.0	19.0
7	**5**	H, Me		5.16	1.0
8	**6**	Me, H		15.1	2.9
9	**7**	H, Me		4.64	0.9

[a] Second-order rate constants were obtained by dividing the pseudo-first-order rate constants k_{obs} (at 30 °C in $CDCl_3$) by the catalyst concentration (0.296 M). [b] Completely inverted into the corresponding *β*-isomer. [c] The *k* values at different temperatures (60 and 70 °C) are 7.66 and 23.2 (× 10^{-5} s^{-1}), respectively, and give the extrapolated *k* value of 2.18 (× 10^{-6} s^{-1}) at 30 °C as well as the activation parameters ($\Delta H^{\ddagger} = 97.9$ kJ mol^{-1}, $\Delta S^{\ddagger} = -35.3$ J K^{-1} mol^{-1}, $\Delta G^{\ddagger} = 108.6$ kJ mol^{-1} at 80 °C). [d] Calculated from the equilibrium constant (*K* = 0.046 at 80 °C) for **3**α ⇄ **3***β*.

Table 1 indicates that the rates were accelerated or decelerated depending on the conformation (α or *β*) of the dibenzocycloheptene moiety and on the substitution pattern (*p* or *m*) of quinone dimethyl substituents. The most striking feature of the reactions of **3** and **4** is a reversal of the relative reactivity of α- and *β*-conformers. Thus, for **3**, the less stable α-conformer was ca. 4 times more reactive than the stable *β*-conformer (entries 3 and 4), whereas for **4** the stable *β*-conformer was ca. 25 times more reactive than the less stable α-conformer (entries 5 and 6) Additionally, the noticeable points are as follows: (1) the conformationally locked **3** and **4** (except **4***β*) exhibited the reactivity comparable to that for the related **5** and **6**, and (2) the *m*-dimethyl-substituted **4** and **6** tended to react faster than the *p*-dimethyl-substituted **3** and **5** (entries 3−8).

These appreciable conformational effects can be explained by assuming that the present acid-mediated regioselective oxirane ring opening occurs via a S_N2-like concerted mechanism.[2] Indeed, the concerted mechanism was strongly supported by the poor kinetic solvent effects in the $MeSO_3H$-mediated reaction of epoxide **5**[8] as well as the appreciable kinetic substituent effects.[9] Specifically, it can be envisaged that the reaction proceeds through the stereoelectronically controlled *π*-aryl participated rate-determining transition state with the aid of the vacant oxirane Walsh orbital (LUMO)[10] as depicted in Figure 1. Here, we can also imagine that the *π*-aryl participation would be significantly intensified in the conformers in which the approaching aromatic *π*-orbital (HOMO) performs the ideal head-to-head orbital overlapping with the oxirane Walsh orbital. Such a through space orbital interaction is favorably achieved for the conformers **3**α and **4***β* (Figure 1, a and d), overriding the high inversion energy cost (>108 kJ mol^{-1}). This is a reason for the higher reactivity of **3**α and **4***β* than the corresponding isomers **3***β* and **4**α, respectively. By contrast, the corresponding orbital interaction for the less reactive conformers **3***β* and **4**α is considerably reduced due to the rather insufficient orthogonal orbital interaction (Figure 1, b and c), thus lowering the reactivity irrespective of requiring no conformational inversion.

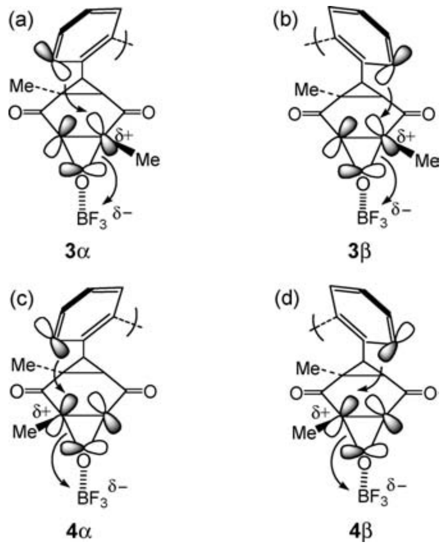


Figure 1. A possible orbital interaction between HOMO (aromatic ring) and LUMO (Walsh orbital of epoxide) in transition states: (a, d) favorable interaction for **3**α and **4***β* and (b, c) less favorable interaction for **3***β* and **4**α. For clarity, the ethano-bridge and the exoaromatic ring are omitted.

Accordingly, the 25-fold higher reactivity of the stable **4***β* compared with that of **4**α can be taken as strong evidence for the occurrence of favored *π*-electron-donating interaction with the oxirane vacant Walsh orbital as depicted in Figure 1d. As to **3**α, however, the rather diminished 3.5-fold higher lability compared with that of the *β*-isomer may be due to

---

(7) Weissensteiner, W.; Hofer, O.; Wagner, U. G. *J. Org. Chem.* **1988**, *53*, 3988.

the additional steric interaction between the cyclopropane Me substituent and the *exo*-aromatic ring (B). As a result, the rates of epoxide ring opening of **3** and **4** are goverened by the critical balance between the attractive π-aryl participated orbital interaction and the repulsive van der Waals congestion associated with the conformational inversion of dibenzocycloheptene ring.

Incidentally, alternative S_N1-like two-step mechanism may contradict the present kinetic results because the more reactive conformers **3**α and **4**β have the capturing aryl orbital unfavorably reacting across the ring system to engage the carbocation p-orbital (rehybridized from the Walsh orbital), whereas the less reactive **3**β and **4**α enjoy the capture on the same side of the ring system. This would predict the result opposite to that deduced from the consideration of Walsh orbital.

In summary, based on the kinetics and conformational effects in acid-mediated reactions of the present homobenzoquinone epoxides, we have found that the π-aryl participated electron-donating interaction with the vacant oxirane Walsh orbital plays a prominent role in the epoxide ring opening. The present findings will provide very useful insights into the mechanistic understanding of the acid-catalyzed ring opening of epoxides.

Acknowledgment. H.A. expresses special thanks for The Global COE (center of excellence) program "Global Education and Research Center for Bio-Environmental Chemistry" of Osaka University.

Supporting Information Available: Selected spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800535C

---

(8) Oshima, T.; Asahara, H.; Koizumi, T.; Miyamoto, S. *Chem. Commun.* **2008**, *15*, 1804.

(9) A preliminary kinetic study indicated that the introduction of *p*,*p*′-dimethyl or *p*,*p*′-dichloro substituents results in an approximately 11-fold increase or 33-fold decrease in the rate of the parent epoxide **5**; further details will be described elsewhere.

(10) (a) Mollere, P. D.; Houk, K. N. *J. Am. Chem. Soc.* **1977**, *99*, 3226. (b) Iwamura, H.; Sugawara, T.; Kawada, Y.; Tori, K.; Muneyuki, R.; Noyori, R. *Tetrahedron Lett.* **1979**, 3449. (c) Bach, R. D.; Wolber, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1410.