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On the Mechanism of the Stereo- and Regioselective Ether-ring Opening of 1,2,3,4-Tetrahydro-1β,4β-epoxy-2α,3α-carbonyldioxy Arene Systems with Boron Tribromide

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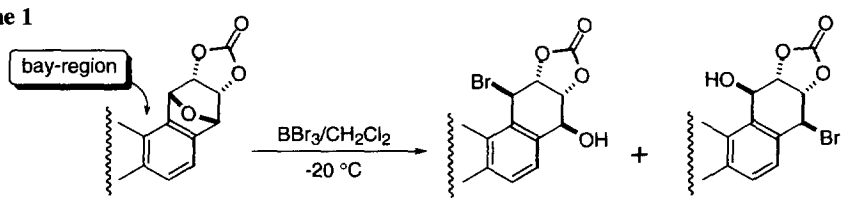
Abstract: Stereo- and regioselective formation of bay-region bromo alcohols observed during ether-bridge opening of the titled systems with boron tribromide has been rationalized, on the basis of AM1 calculations, by the intramolecular same-face delivery of the bromide ion from the intermediate borate group and the relative stability of the bay-region versus non-bay-region benzylic cations, respectively.

The biological activity of carcinogenic polycyclic aromatic hydrocarbons (PAHs) has been demonstrated to, in systems containing a bay-region, originate from bay-region diol epoxide metabolites of the parent PAHs.[1] Accordingly, access to such metabolites through synthesis has become of prime importance for the study of the molecular mechanism of chemical carcinogenesis by PAHs having the bay region.[2] To this end, we have recently developed a new, generally applicable synthetic method toward these bay-region diol epoxides.[3] One of the key steps in this methodology involves a highly stereo- and regioselective ether-ring opening of 1,2,3,4-tetrahydro-1β,4β-epoxy-2α,3α-carbonyldioxy arene systems with boron tribromide, i.e., **1** → **2** in Scheme 1. The bromo alcohol intermediates **2**, where the halogen-leaving group is introduced in the

Scheme 1



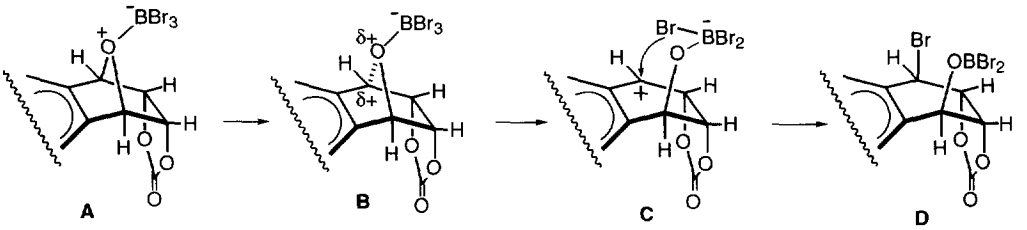
1 **2** **3**

bay-region and trans to the homobenzylic hydroxyl equivalent, have served as the crucial precursors to the bay-region diol epoxide metabolites of PAHs.[3] In this communication, we postulate the mechanism of this

highly stereo- and regioselective ether-ring opening reaction with particular emphasis on the use of results of AM1 calculations to account for the regioselectivity of the ether-bridge opening.

A proposed mechanism for the ether-ring opening is summarized in Scheme 2. While coordination of BBr_3 on the cyclic carbonate group should take place to a significant extent reversibly, that of the Lewis acid with the benzylic ether-bridge oxygen is likely to induce the weakening of the benzylic C-O bond (see **B**). This weakening of the benzylic C-O bond would ultimately result in the cleavage of the bond to give rise to a benzylic cabocation in intermediate **C**. When the ether-bridge compound is unsymmetrical with respect to the aromatic portion, regioselectivity to be observed in the ring-opening should be a manifestation of the relative ease with which each of the two benzylic C-O bonds is cleaved. This, in turn, is likely to be predicated upon the extent to which the developing benzylic carbocation **B** can be accommodated in either the bay region or the non-bay region. The formation of the benzylic C-Br bond with retention of stereochemistry of the original

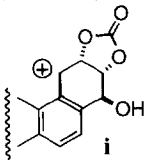
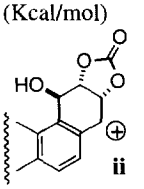
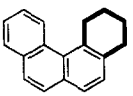
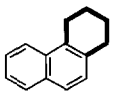
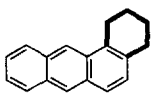
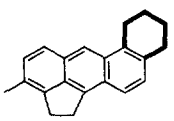
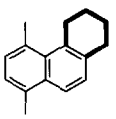
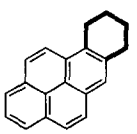
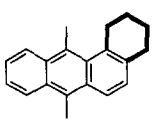
Scheme 2.



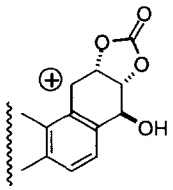
benzylic C-O bond may be rationalized by invoking an intramolecular, same-face delivery of the bromide anion from the borate group (see **C** → **D** in Scheme 2).

The "bay-region theory" put forward by Jerina and Lehr in an attempt to account for the chemical carcinogenicity of bay region-containing PAHs is based on the higher stability of the bay-region benzylic carbocation over the corresponding non-bay region carbocation.[4] This difference in stability had been deduced from the results of simple perturbational molecular orbital calculations for unsubstituted PAH skeletons. In light of this hypothesis, the predilection for the regioselective formation of the bay-region bromide upon ether-bridge opening is not entirely unexpected. However, considerable difference in the regioselectivity observed for the ether-bridge opening between alkyl-substituted PAH and its parent PAH (see, e.g., entries 2 and 5 in Table 1) can not be accounted for by the above-mentioned bay-region theory since it is based on calculations that involve only aromatic π-electrons. Therefore, in an effort to better correlate the observed regioselectivity among various PAHs including those with alkyl substituents with the relative stabilities of the bay-region and its corresponding non-bay region benzylic carbocations, the heats of formation have been calculated for these carbocations **i** and **ii** with the use of a semi-empirical molecular orbital AM1 method[5] for several PAH systems. Thus, starting geometries of **i** and **ii** were preoptimized using PCMODEL (Serena Software, Bloomington, Indiana, USA) which includes an MMX force field optimization. The geometries were further optimized in terms of bond lengths, bond angles, and dihedral angles and the heats of formations were obtained with a restricted Hartree-Fock calculation (RHF) using standard AM1 parameters with the PRECISE option as implemented on MOPAC, version 6.0[6] on a Silicon Graphics 4D/360 workstation.[7]

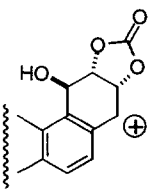
Table I. Results of AM1 Calculations on the Stability of Bay- and Non-Bay-region Benzylic Cations and Correlation with Observed Regioselectivity

entry	PAH[a]	ΔH_f (bay) carbocation **i** (Kcal/mol)  **i**	ΔH_f (non-bay) carbocation **ii** (Kcal/mol)  **ii**	$\Delta\Delta H_f$ = ΔH_f (bay)- ΔH_f (non-bay) (Kcal/mol)	Observed selectivity[b] (bay : non-bay)
1		102.81	104.89	-2.08	2.8 : 1[c]
2		81.88	85.52	-3.64	4.5 : 1[d]
3		100.82	104.66	-3.84	NA
4		91.97	97.25	-5.28	NA
5		89.31	96.40	-7.09	≈30 : 1[d]
6		97.67	112.14	-14.47	>50 : 1[e]
7		90.51	122.83	-32.32	>50 : 1[e]

a. The bold-faced bonds indicate the tetrahydrobenzo ring with the carbonate and hydroxyl groups and the benzylic carbocation at the bay (structure **i**) or non-bay (structure **ii**) position.
b. Experimentally observed ratios (determined by the NMR analysis of the crude product mixture) of the regioisomeric bromo alcohols as shown in Scheme I.
c. Unpublished results.
d. Reference 3a.
e. Reference 3b. Analysis of the proton NMR (360 MHz) spectrum of the crude reaction products revealed the presence of the bay-region bromo alcohol as a single isomer.



bay-region carbocation **i**



non-bay-region carbocation **i**

The results of the AM1 calculations summarized in Table 1 show the difference in the heats of formation ($\Delta\Delta H_f$) between the bay-region benzylic carbocation **i** and its corresponding non-bay region counterpart **ii** for a given PAH system. There seems to exist a reasonably good correlation between the values of $\Delta\Delta H_f$ and the observed ratios of the bay- and non-bay region bromides as indicated in Table 1. It should be noted that in these calculations the fully developed carbocation structures have been employed to approximate their respective incipient transition state structures; the energies of these carbocations **i** and **ii** have been used as approximations to those of the corresponding transition states. Accordingly, the magnitude of $\Delta\Delta H_f$ as such should not be expected to exactly correspond numerically to the experimental ratios of the bromide formation. However, the general trend that the larger the difference in the stabilities of the two cations (i.e., the larger $|\Delta\Delta H_f|$), the greater regioselectivity in the ether-bridge opening is readily apparent. These values of $\Delta\Delta H_f$ should provide a practical scale of index with which the regioselectivity for the ether-bridge opening may be predicted for a given PAH prior to experimentation.

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References and Notes

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6. Stewart, J. J. P. *QCPE* **1990**, *10*, 9 and **1985**, *5*, 455.
7. The lowest-energy conformations of the tetrahydrobenzo ring in **D** in all of the bay-region containing PAH systems examined have been calculated to adopt the boat forms as indicated in Scheme 2. Therefore, the transition state for the transformation **C** → **D** is likely to resemble a boat form rather than the half-chair form for the tetrahydrobenzo ring as postulated in our earlier publication (see Ref 3a).

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