Sterically Induced Methoxyl Migration on Acid-Catalyzed Dehydration of K-Region *trans*-Dihydrodiol Monomethyl Ethers

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The regioisomers of the *trans*-dihydrodiol monomethyl ethers (DME) at the K-regions of 4- and 7-methyl- and 7,12-dimethylbenz[*a*]anthracene, which possess a ring methyl substituent *peri* to the methoxyl group, react with BF_3-etherate to form a single phenol and two regioisomeric phenol methyl ethers, one of which arises by migration of the methoxyl group. In contrast, for DME of benz[*a*]-anthracene and its 1-, 4-, 7-, 11- and 12-methyl- and 7,12-dimethyl-substituted derivatives where there is no *peri* methyl group, methoxyl migration does not occur, and thus only the phenol methyl ether resulting from loss of water is formed. These results are consistent with a mechanism in which the initially formed carbocation with a pseudoaxial methoxyl group must undergo either conformational change to align the bond of the leaving proton with the empty p-orbital prior to proton loss or migration of the methoxyl group to the adjacent carbocation *via* a cyclic oxonium ion. In the absence of a ring substituent *peri* to the methoxyl group, conformational change is faster than formation of the cyclic oxonium ion, and therefore migration of the methoxyl group does not occur. A methyl substituent *peri* to the methoxyl group raises the activation energy barrier for conformational isomerization due to adverse steric interaction between the two groups. Consequently, formation of the cyclic oxonium ion becomes competitive with conformational change. The resulting oxonium ion opens to the regioisomeric carbocation resulting in rearrangement. Formation of the cyclic oxonium ion in these reactions is analogous to the rapid internal return of the hydroxy carbocation intermediate to protonated epoxide that is thought to occur in the reactions of *peri*-methyl-substituted K-region arene oxides.

Introduction

We have recently proposed the mechanism shown in Scheme I for acid-catalyzed reactions of K-region arene oxides.[1-3] In this mechanism, the initially formed carbocation with a pseudoaxial hydroxyl group (conformation I) either reacts with a nucleophilic solvent molecule to produce cis- and trans-addition products (k_4), recyclizes to the protonated arene oxide (k_{-2}), or undergoes conformational change to carbocation conformation II (k_3). Once formed, conformation II, which has an axial C-H bond properly oriented to overlap with the empty p-orbital of the adjacent sp^2 carbon, undergoes a rapid 1,2-hydride shift to form a ketone, whereas conformation I does not undergo hydride migration. The ketone enolizes to the corresponding phenol in a subsequent step. According to this mechanism, if trapping (k_4) of the carbocation is impossible (as in a non-nucleophilic solvent), a change in rate-determining step from epoxide ring opening (k_2) and its reversal to conformational inversion (k_3) of the carbocation will occur when conformational inversion is made sufficiently difficult. We proposed that steric effects arising from substitution at a position *peri* to the K-region bring about such a change in rate-determining step in acetonitrile.[3] In this non-nucleophilic solvent, the carbocation is forced to choose between the conformational change that leads to phenol product or reclosure of the epoxide ring to give the protonated starting material. For carbocations formed from most arene oxides, the activation energy for the conformational change (k_3) is lower than that for the ring closure (k_{-2}), and epoxide ring opening is rate-limiting. In contrast, the steric constraint imposed by a ring methyl substituent *peri* to the hydroxyl group of the carbocation alters the relative heights of the two energy barriers, so that conformational isomerization becomes rate-limiting. In such a case, protonated arene oxide could undergo several ring openings to carbocation conformation I and reclosures before undergoing the requisite conformational change that leads to products.[3] Notably, cis-trans isomerization of deuterium at the nonbenzylic position of *p*-methoxystyrene oxide, at a rate that is faster than its overall reaction to give diol and carbonyl rearrangement product, has been demonstrated and was ascribed to the rapid reversibility of epoxide ring opening, relative to subsequent reaction steps.[4] Because the rigid hydrocarbon ring system of the K-region arene oxides prevents rotation around the C-C bond of the hydroxy carbocation, direct demonstration of reversible oxirane ring opening in these compounds by a similar technique is not possible.

As a test of the mechanism of Scheme I, we envisioned the use of methoxyl carbocations formed by loss of a hydroxyl group from K-region *trans*-dihydrodiol monomethyl ethers (DMEs) as models for the hydroxy carbocation intermediates in K-region arene oxide solvolysis and rearrangement. The regiospecific generation of these methoxyl carbocations from isomeric DMEs is possible since dehydration of these monomethyl ethers with BF_3-etherate is known to involve preferential elimination of water to produce the corresponding phenol methyl

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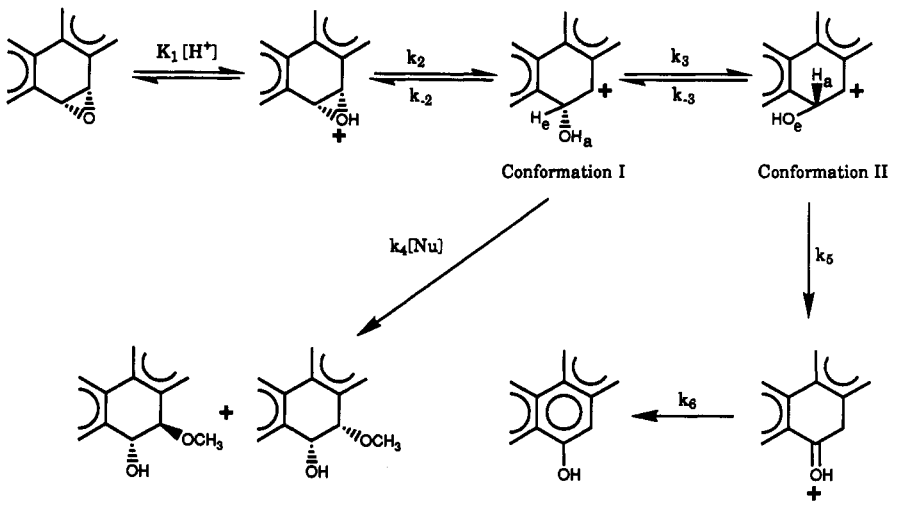
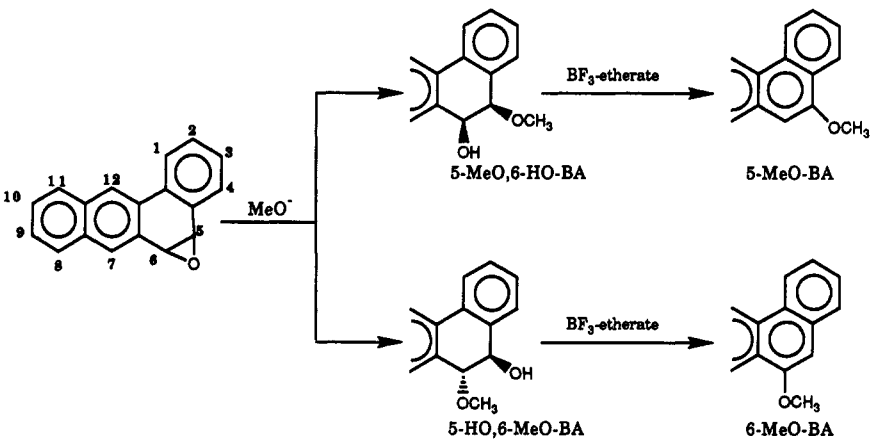
0022-3263/93/1958-6344$04.00/0

Scheme I



Scheme II



ethers[5] (cf. Scheme II). The reaction is thought to proceed by coordination of BF_3 to the hydroxyl group followed by cleavage of the C–OH bond to form a methoxyl carbocation. Subsequent loss of a proton gives the phenol methyl ethers. Normally, rearrangement of the methoxyl group does not occur. Following the mechanism in Scheme I, we predicted that, for methoxyl carbocations with a ring substituent *peri* to the K-region methoxyl group, internal ring closure to the methoxonium ion (analogous to the protonated epoxide) should be faster than overall product formation if the proton abstraction that leads to product requires a conformational change. The proposed oxonium ion could open to the regioisomeric carbocation, which has no steric barrier to conformational inversion and thus would readily undergo conformational change and proton loss to give a product in which methoxyl migration has occurred. In the present study, we examine the reaction of BF_3·etherate with the regioisomeric DMEs of benz[*a*]anthracene (BA) and its 1- (1-MBA), 4- (4-MBA), 7- (7-MBA), 11- (11-MBA), and 12-methyl- (12-MBA) and 7,12-dimethyl-substituted (DMBA) derivatives.

Results and Discussion

Under the conditions reported previously for the dehydration of DMEs with BF_3·etherate,[5] several of the phenol methyl ether products are unstable. Under the present conditions (dark, ambient temperature, anhydrous) product compositions remained unchanged throughout the time course of the reactions as evidenced by HPLC. Control experiments showed that product phenol methyl ethers and phenols were stable when incubated under the reaction conditions for the time required to convert ~90% of the starting material to products. Anhydrous conditions were maintained since both the rate and product distribution for the reaction of 5-HO,6-MeO-7-MBA were found to be sensitive to the presence of water.[6] Table I summarizes the results of the reaction of BF_3·etherate with isomeric DMEs of BA, 1-MBA, 4-MBA, 7-MBA, 11-MBA, 12-MBA, and DMBA.

With the exception of 5-MeO,6-HO-4-MBA, 5-HO,6-MeO-7-MBA, and 5-HO,6-MeO-DMBA, the BF_3·etherate reaction produced a single, unrearranged phenol methyl ether by the elimination of water in quantitative yield. Thus, there is a large preference for elimination of water over methanol from these DMEs. In contrast, the above DMEs with ring methyl substituents *peri* to the methoxyl groups produced regioisomeric K-region phenol methyl ethers as well as the phenols whose hydroxyl groups are not in a position *peri* to the ring methyl substituent (cf.

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(6) The rate of reaction is almost doubled by adding 0.75 equiv of water with respect to BF_3–etherate, and the yield of 5-HO-7-MBA increased from 41% to 61% as a result of increased elimination of methanol. 5-MeO-7-MBA was not converted to the corresponding phenol under identical conditions. Above 1 molar equiv of water, the rate decreased, and complete inhibition of reaction was observed in the presence of 2 equiv of water, probably due to the formation and precipitation of $(BF_2{\cdot}(H_2O)_2)F$.

Table I. Conditions and Products for Reactions of BF_3-Etherate with K-Region *trans*-Dihydrodiol Monomethyl Ethers of Benz[*a*]anthracene

compd	BF_3-ether,[a] μL	reactn time, h	product % 5-MeO	product % 6-MeO	% phenol	% conversn
5-MeO,6-HO-BA	250	5	100			>95
5-HO,6-MeO-BA	250	5		100		>95
5-MeO,6-HO-1-MBA	250	4	100			>95
5-HO,6-MeO-1-MBA	250	3		100		>95
5-MeO,6-HO-4-MBA	250	6	75	20	5[b]	>95
5-HO,6-MeO-4-MBA	250	5		100		>95
5-MeO,6-HO-7-MBA	250	5	100			>95
5-HO,6-MeO-7-MBA	250	5	32	27	41[c]	90[d]
5-MeO,6-HO-11-MBA	250	5	100			90[d]
5-HO,6-MeO-11-MBA	250	5		100		86[d]
5-MeO,6-HO-12-MBA	250	24	100			>95
5-HO,6-MeO-12-MBA	400	24		100		70[d]
5-MeO,6-HO-DMBA	250	4	100			>95
5-HO,6-MeO-DMBA	250	6	30	30	40[c]	85[d]

[a] Volume of BF_3-ether added to 1 mL of a solution of DME in ether. [b] The phenolic hydroxyl at C_6. [c] The phenolic hydroxyl at C_5. [d] The balance is starting material.

Table I). These phenols must result from the elimination of methanol from the DMEs, since methyl ethers do not demethylate under the reaction conditions.

Two pathways are possible for formation of the apparent rearrangement products (6-MeO-4-MBA, 5-MeO-7-MBA, and 5-MeO-DMBA) from the reaction of 5-MeO,6-HO-4-MBA, 5-HO,6-MeO-7-MBA, and 5-HO,6-MeO-DMBA with BF_3-etherate, namely, (i) intramolecular migration of a methoxyl group in the intermediate carbocation or (ii) reaction of methanol with 6-HO-4-MBA, 5-HO-7-MBA, and 5-HO-DMBA to form methyl ethers.[7] The low to moderate amounts of these phenols observed in the product mixtures are presumed to arise by elimination of methanol from the DMEs (cf. Table I). In order to distinguish between methoxyl migration and O-methylation of phenols, reaction of 5-HO,6-MeO-7-MBA was investigated in the presence of 1 molar equiv of ^{18}O-labeled methanol (isotopic purity 98.7%) per mol of BF_3-etherate. This amount of methanol represented a large molar excess over the substrate and would thus dilute out any unlabeled methanol formed by elimination. If 5-MeO-7-MBA were formed from the 6-methoxyl carbocation by intramolecular methoxyl migration, no labeled oxygen would be incorporated, whereas if this product arose exclusively by reaction of methanol with 5-HO-7-MBA, 100% incorporation of the ^{18}O label is predicted. The two regioisomeric phenol methyl ethers were isolated, and mass spectrometric analysis indicated that, as expected, no label was incorporated into the unrearranged product 6-MeO-7-MBA. Similarly, 64% of the isolated 5-MeO-6-MBA did not incorporate ^{18}O from added methanol and thus *must have arisen from methoxyl migration.* The remainder of the 5-methyl ether (34%) contained ^{18}O; this could, however, be attributed to a secondary reaction of 5-HO-7-MBA with methanol. Incubation of 5-HO-7-MBA (formed by dehydration of the K-region *cis*-dihydrodiol) with BF_3-etherate in the presence of the same molar excess of methanol used in the isotope incorporation experiment for a time corresponding to ~90% reaction of 5-HO,6-MeO-7-MBA gave only ~50% conversion of the phenol to its methyl ether. It should be noted that the secondary reaction of 5-HO-7-MBA with methanol under the conditions of dehydration of DME should not be significant since so little methanol is formed during the reaction. Exchange of labeled methanol into unlabeled 5-MeO-7-MBA did not occur when the phenol methyl ether was incubated with BF_3-etherate and 1 molar equiv of ^{18}O-labeled methanol for 7 h. These results clearly demonstrate that, under the present dehydration conditions, 5-MeO-7-MBA is formed predominantly, if not exclusively, *via* intramolecular rearrangement of the intermediate carbocation and not by a secondary reaction of the product phenol with methanol.

On the basis of the foregoing results, we propose the mechanism in Scheme III for the dehydration of K-region DMEs. This mechanism is closely analogous to that shown in Scheme I for acid-catalyzde reactions of K-region arene oxides. Specifically, Lewis-acid catalyzed loss of the hydroxyl group occurs preferentially from the pseudodiaxial conformation of the DME to form a carbocation with a pseudoaxial methoxyl group. Elimination of an axial substituent should be facilitated by alignment of the incipient empty p-orbital with the neighboring aromatic π-system. For example, the K-region *cis*-dihydrodiol of phenanthrene, in which one of the hydroxyl groups must be pseudoaxial, undergoes acid-catalyzed dehydration 112 times faster than the trans isomer, which prefers the pseudodiequatorial conformation for its hydroxyl groups.[8] The initially formed carbocations from arene oxides (Scheme I) and the DMEs (Scheme III) are both expected to have conformation I. In this conformation, the C–H bond that must be cleaved to yield the eventual product is almost perpendicular to the empty p-orbital. Thus, conformation I must undergo isomerization to conformation II, in which the C–H bond is coplanar with the empty p-orbital, in order for either hydride migration (Scheme I) or proton abstraction and aromatization (Scheme III) to occur. Once carbocation conformation II is formed, it is committed to product formation since subsequent steps (proton abstraction or hydride migration) are fast. Thus, in the arene oxide reactions (Scheme I) the partitioning of conformation I of the hydroxy carbocation between conformational change and return to protonated epoxide is determined by the relative values of k_{-2} and k_3. If $k_{-2} < k_3$, carbocation formation is the rate-determining step, whereas if $k_{-2} > k_3$, the conformational change is rate-

(7) (a) Yagi, H.; Holder, G. M.; Dansette, P. M.; Hernandez, O.; Yeh, H. J. C., LeMahieu, R. A.; Jerina, D. M. *J. Org. Chem.* **1976**, *41*, 977. (b) Newman, M. S., Sankaran, V.; Olson, D. R. *J. Am. Chem. Soc.* **1976**, *98*, 3237. (c) Wiley, J. C., Jr.; Menon, C. S.; Fischer, D. L.; Engel, J. F. *Tetrahedron Lett.* **1975**, 2811.

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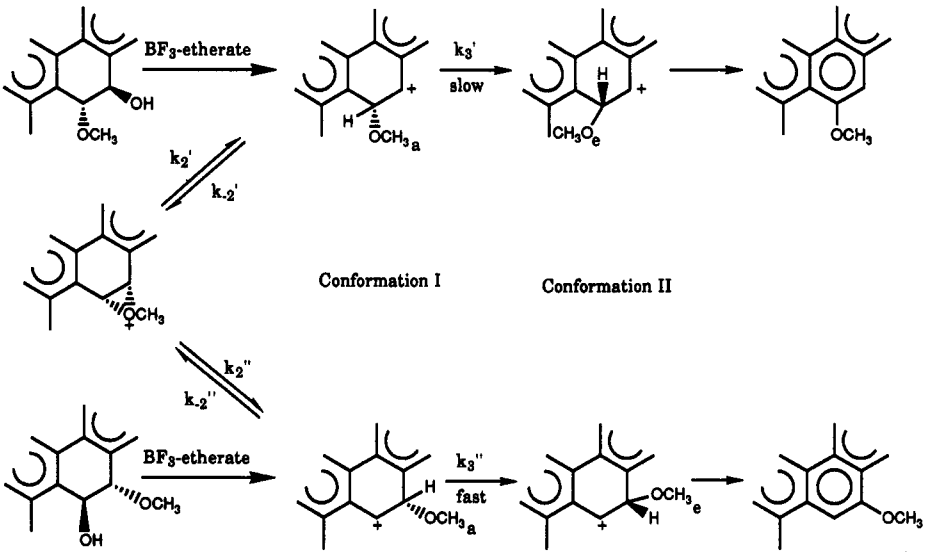
Scheme III



determining. Analogous processes for the methoxyl carbocations are shown by the primed rate constants in Scheme III. In this case partitioning of conformation I between conformational inversion and methoxonium ion formation determines whether methoxyl migration will occur in the course of reaction. If $k_3' < k_{-2}'$ the cyclic methoxonium ion (analogous to the protonated epoxide) will form and can subsequently react *via* the lower pathway (k_2'') to give rearranged product.[9]

For hydroxy carbocations that have no methyl substituent in the bay region or *peri* to the hydroxyl group, the energy barrier for conformational isomerization is low relative to that for recyclization to the protonated epoxide.[1-3] As previously observed, this situation corresponds to rate-determining epoxide ring opening (cf. Scheme I, $k_3 > k_{-2}$). All the DMEs that yield analogous methoxyl carbocations were dehydrated to produce exclusively the unrearranged K-region phenol methyl ethers (lower pathway of Scheme III, $k_3'' > k_{-2}''$).

On the other hand, a methyl substituent in a position *peri* to the methoxyl or hydroxyl group of a carbocation is expected to increase the energy barrier for conformational isomerization (k_3') due to steric effects and have little or no effect on ring closure (k_{-2}') to a cyclic oxonium ion.[1-3] For rearrangements of K-region arene oxides in acetonitrile, this steric effect was proposed to cause a change in rate-determining step from formation of the hydroxy carbocation to its conformational inversion (Scheme I, $k_3 < k_{-2}$). With the present methoxyl carbocations, an analogous decrease in k_3' causes cyclization to be competitive in rate with conformational isomerization, and products are observed from both reaction pathways. The dual reaction pathway is indicated by the fact that compounds 5-HO,6-MeO-7-MBA and 5-HO,6-MeO-DMBA produce equal amounts of the regioisomeric products (cf. Table I), even though the carbocation at C_6 is significantly more stable than that at C_5.[2] Even more strikingly, the isomers of these two compounds, 5-MeO,6-HO-7-MBA and 5-MeO,6-HO-DMBA, gave only direct dehydration product and thus could not have reacted *via* the same intermediate as their positional isomers. Thus, the cyclic oxonium ion is not a compulsory intermediate in these reactions. In contrast, the cyclic episulfonium ion intermediate in the dehydration of thiol adducts of K-region arene oxides is a compulsory reaction intermediate as demonstrated by the observation of products in a ratio corresponding to the relative stabilities of the positionally isomeric carbocations regardless of the original position of sulfur substitution.[10]

Hydrocarbons with a methyl group in the bay region such as DMBA, 1-MBA and 12-MBA, and their K-region arene oxides are known to be significantly distorted from planarity due to steric interaction between the bay-region hydrogen, i.e., H_1 or H_{12} and the methyl substituent.[2,11] Such a steric effect has been shown to slow down the rate of the conformational isomerization of K-region *cis*-dihydrodiol dimethyl ethers because the planar transition state brings the bay-region hydrogen and the methyl group into closer steric contact.[1] Thus, it was anticipated that K-region hydroxy or methoxy carbocations derived from these bay-region-substituted hydrocarbons would have higher energy barriers for conformational isomerization than their unsubstituted analogs. The present results for the DME's with a methyl substituent in the bay region indicated that only dehydration products without rearrangement are formed. Thus, as in the case of the unsubstituted DMEs, cyclization of the initially formed methoxyl carbocation must be slow relative to its conformational inversion. This observation is consistent with the hypothesis that these bay-region substituted carbocations have higher energy barriers for *both conformational isomerization and cyclization* because the planar transition states for both of these processes are more strained than the nonplanar carbocations. Thus, the effect of methyl substitution in the bay region on k_{-2}' and k_3' is similar, and the *relative* heights of the energy barriers for these two steps are similar to those for the unsubstituted compounds. An analogous argument has been proposed to explain the observation that carbocation formation, rather than conformational inversion, is rate-determining for ketone formation from the K-region arene oxides of DMBA, 1-MBA, and 12-MBA in acetonitrile, just as it is

(9) As an alternative to the loss of a proton from a rearranged open carbocation, one of the reviewers has suggested that elimination of a proton accompanied by breaking of a C–O bond is a plausible mechanism for the direct formation of products from the cyclic oxonium ion.

(10) Balani, S. K.; Sayer, J. M.; Jerina, D. M. *J. Am. Chem. Soc.* **1989**, *111*, 3290.

(11) Glusker, J. P.; Carrell, H. L.; Zacharias, D. E.; Harvey, R. G. *Cancer Biochem. Biophys.* **1974**, *1*, 43.

for the arene oxides that lack methyl substitution, despite the relatively slow conformational inversion expected for these hydroxy carbocations.[3]

The observation of rearrangement products from the reactions of 5-MeO,6-HO-4-MBA, 5-HO,6-MeO-7-MBA, and 5-HO,6-MeO-7-DMBA with BF_3·etherate provides direct and independent experimental evidence in support of the mechanism of Scheme I for the acid-catalyzed solvolysis reaction of K-region arene oxides in which steric effects are a dominant influence on both product distribution and rate-determining step. Notably, migration of ether substituents in dehydration reactions of disubstituted K-region derivatives has not been previously reported, although migrations of thioether[10] and azide[12] substituents are well documented. Methoxyl migration in the present case is a direct consequence of the substantial steric barrier to conformational inversion in the *peri* substituted methyl ethers investigated.

Experimental Section

Materials. The regioisomeric DME of BA, 1-MBA, 4-MBA, 7-MBA, 11-MBA, 12-MBA, and DMBA,[2] 6-HO-4MBA, 5-HO-7-MBA, 5-HO-DMBA,[3] 5-MeO-7-MBA,[2] and isomeric K-region phenol methyl ethers of 1-MBA, 11-MBA, 12-MBA,[2] and DMBA[5b] were obtained as described previously.

Reaction of DME with BF_3·etherate. The method described by Wong et al.[5a] was modified. To a solution of 0.25–1.0 mg of DME in 1 mL of anhydrous ether in a flask purged with nitrogen, at ambient temperature, was added 0.250 mL of BF_3·etherate. The effect of water on the BF_3·etherate reaction was examined with 5-HO,6-MeO-7-MBA. The reaction was carried out as described above except that 0.1–2.0 molar equiv of water with respect to BF_3·etherate were added. A similar reaction was conducted in the presence of 85 μL of $Me^{18}OH$ (equimolar to BF_3·etherate) instead of water. The reactions were followed simultaneously on two Du Pont Zorbax silica columns (0.94 × 25 cm). One was eluted with 1% methanol in 10% ethyl acetate in hexane to monitor the disappearance of the starting material, and the other was eluted with 9% dichloromethane in hexane to monitor the appearance of the K-region phenol methyl ethers. Once most of the starting material had disappeared, the reaction mixture was added to ca. 50 mL of 1:1 ether/H_2O. The ether phase was washed several times with water and dried over $MgSO_4$. After evaporation of solvent, the product composition in the residue was determined by NMR ($CDCl_3$). For reaction of the isomeric K-region DMEs of BA, 1-MBA, 11-MBA, and 12-MBA and 5-HO,6-MeO-4-MBA, 5-MeO,6-HO-7-MBA, and 5-MeO,6-HO-DMBA, only one phenol methyl ether is observed in which the methoxyl group is attached to the same carbon as that of the starting material. With the exception of 6-MeO-4-MBA, all these phenol methyl ethers are known compounds, and their ^1H NMR spectra were compared to those of authentic samples.[2,7c] The structural assignment of 6-MeO-4-MBA is discussed below. Reactions of 5-MeO,6-HO-4-MBA, 5-HO,6-MeO-7-MBA, and 5-HO,6-MeO-DMBA produce both regioisomeric phenol methyl ethers, and the phenol in which the hydroxyl group is not in a *peri* position relative to the ring methyl substituent. All phenols,[3] 5-MeO-7-MBA, and both phenol methyl ethers of DMBA[5b] are known compounds. Other products were purified from the product mixture and characterized as described below. Product ratios were determined by integration of the ring methyl resonances between δ 2.6 and 3.3 ppm and/or the methoxy methyl resonances around δ 4 ppm (cf. Table II). Chemical shifts for the ring methyl groups in the phenolic products 6-HO-4-MBA and 5-HO-7-MBA are 2.60 and 3.00 ppm, respectively. In $CDCl_3$, 5-HO-DMBA is mostly in the keto form and displays two methyl resonances at δ 2.64 and 3.00 ppm.

Product mixtures from the reactions of 5-MeO,6-HO-4-MBA, 5-HO,6-MeO-7-MBA, and 5-HO,6-MeO-DMBA were passed through a short silica column (Sep-pak, Waters Associates) which was eluted with ether. Ether was evaporated, and the residues were chromatographed on Du Pont Zorbax SIL (0.94 × 25 cm) columns eluted with 9% dichloromethane in hexane to separate the isomeric K-region phenol methyl ethers. Table II summarizes the k' values and the chemical shifts of key protons of these phenol methyl ethers. For 5-MeO-4-MBA, 6-MeO-4-MBA, and 6-MeO-7-MBA, HRMS were obtained: calcd for the molecular ion $(C_{20}H_{16}O)^+$, 272.1201; found 272.1191, 272.1195, and 272.1196, respectively. The structural assignment of isomeric K-region phenol methyl ethers was based on the downfield shift for protons in *peri* positions relative to a methyl or methoxyl ring substituent.[1,2,5b] For example, the phenol methyl ethers of 4-MBA show a singlet for H_7 at δ 8.10 and 8.86. The isomer displaying the lower field resonance H_7 was assigned the structure 6-MeO-4-MBA because of the expected downfield shift for H_7 caused by the *peri* methoxyl group.

Table II. Chromatographic Separation and Partial NMR Spectra ($CDCl_3$) of Phenol *O*-Methyl Ethers

		chemical shifts (δ, ppm.)						
compd	k' [a]	H_1	H_5	H_6	H_7	H_{12}	OCH_3	CH_3
5-Me-BA[b]		8.74[c]		6.96	8.15	9.00	4.06	
6-Me-BA[b]		8.67[d]	6.81		8.78	9.06	4.09	
5-Me-4-MBA	1.72	8.65[c]		6.94	8.10	8.98	3.98	2.87
6-Me-4-MBA	2.34	8.64[d]	7.01		8.86	9.15	4.17	2.71
5-Me-7-MBA[b]	2.63	8.76[c]		7.18		8.95	4.09	2.97
6-Me-7-MBA	2.19	8.63[d]	6.81			8.98	4.00	3.26
5-Me-DMBA	1.92	8.37[c]		7.07			4.06	3.25, 2.94
6-Me-DMBA	1.68	8.31[b]	6.73				4.03	3.18, 3.25

[a] Chromatographed on Du Pont Zorbax silica columns (0.94 × 25 cm) eluted with 9% dichloromethane in hexane. [b] Results from ref 2. [c] d, J = 8.1–8.3 Hz. [d] Multiplet.

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