5816 *J. Org. Chem.* 1988, *53*, 5816–5819

A Stereospecific, Silver(I)-Assisted Solvolysis of Cyclic Halo Ethers. Evidence for a Push–Pull Mechanism Involving Neighboring Group Participation[†]

Pavel Kočovský

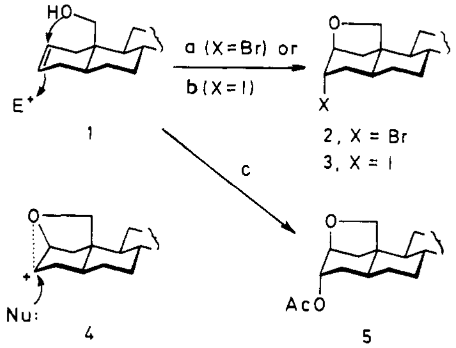
Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6, Czechoslovakia

Received April 15, 1988

A silver(I) ion promoted, stereospecific Koenigs–Knorr-type substitution of halogen atom for hydroxy or alkoxy groups converts cyclic halo ethers (**2** or **3**) to hydroxy (**6**) or alkoxy (**7**, **8**) derivatives with an overall retention of configuration. The reaction is anchimerically assisted by the ether oxygen, which must be antiperiplanarly oriented to the C–Hal bond to be cleaved. Halo lactones **21–23** are inert as well as those halo ethers (**17–19**) that would produce highly strained transition states.

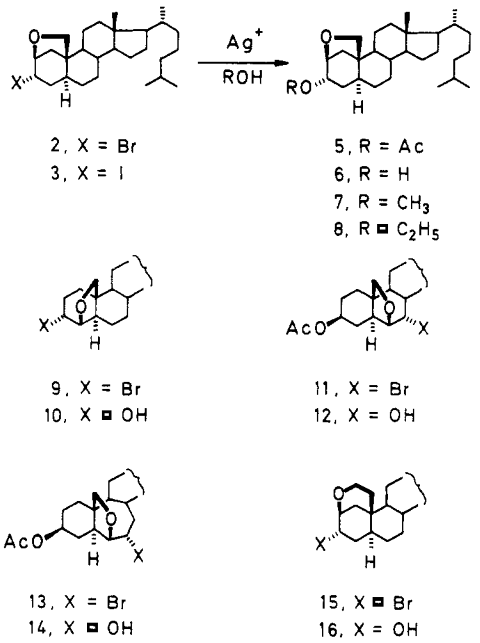
Controlling reactivity by neighboring groups has the promise of enhancing stereoselectivity and of achieving goals that cannot be attained by other methodology. The effects of neighboring groups are particularly manifested in electrophilic additions[1] and nucleophilic substitutions.[2] Thus, for instance, bromination of unsaturated alcohols leads, in suitable instances, to the formation of corresponding cyclic halo ethers (see, e.g. **1** → **2** in Scheme I). This reaction creates two new chiral centers with up to 100% stereo- and regioselectivity. Here we show that the halogen atom in certain halo epoxides thus formed can be replaced with retention of configuration by OH or OR groups.

Scheme I[a]



[a] (a) $CH_3CONHBr$, $HCLO_4$, H_2O, dioxane, room temperature, 10 min; (b) I_2, AcOAg, AcOH, DME, room temperature, 30 min

Scheme II[a]



[a] **5** (71%), **6** (73% from **2**; 69% form **3**), **7** (85%), **8** (64%), **10** (78%), **12** (47%), **14** (84%), **16** (92%).

Results

Hydroxy olefin **1** is known to produce cyclic bromo ether **2** on reaction with hypobromous acid in quantitative yield.[3] In contrast, iodination performed in the presence of silver ions under the Woodward–Prêvost conditions[4] in acetic acid leads to acetoxy ether **5**.[5] Earlier we have tentatively rationalized this reaction outcome assuming substitution of iodine in a transiently formed iodo ether **3** by the solvent.[5] We have proposed a mechanism involving participation of the ether oxygen via ion **4** to account for the observed high stereospecificity of this process.

Now we have found that silver(I)-assisted iodination of **1** carried out in DME/H_2O and/or DME/CH_3OH gives rise to the corresponding hydroxy and/or methoxy ethers **6** (74%) and **7** (69%), respectively (Scheme II). Since the assumed intermediary iodo ether could not be isolated, we turned our attention to its bromo analogue **2**, which in turn was prepared by addition of HOBr to the same starting unsaturated alcohol **1**. To our delight, the bromo ether followed the proposed reactivity and underwent an instant conversion to **6** or **7** when mixed up with $AgClO_4$ or CF_3COOAg[6] in the corresponding media. Similarly, ethoxy derivative **8** was formed in the presence of ethanol in the reaction media. The iodo ether **3** that was later prepared as a stable, crystalline compound by the thallium(I)-assisted iodination[7] of **1**[8] underwent the same reactions in the presence of silver(I) ions.

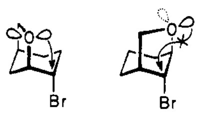
Such a reaction is typical for the acetal carbon of 1-halo sugars and is known as the Koenigs–Knorr glycosylation. However, it seems rather unusual for nonacetal carbons with such a high selectivity.[9] Therefore we set out to establish its scope. The assistance of strongly halophilic silver(I) in pulling out the halogen anion from the molecule of the halo epoxide is obvious,[10] as the cyclic halo ethers **2** and **3** as well as their congeners are stable in the absence

---

[†] Dedicated to Dr. Václav Černý on the occasion of his 65th birthday.

(1) For reviews, see: (a) Kočovský, P.; Tureček, F.; Hájíček, J. *Synthesis of Natural Products: Problems of Stereoselectivity*; CRC: Boca Raton, FL, 1986; Vol. I and II. (b) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed; Academic: New York, 1984; Vol. 3, p. 411. (c) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3. (d) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171.

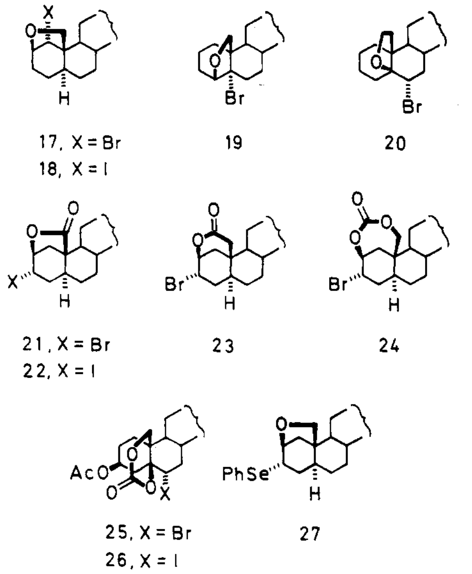
0022-3263/88/1953-5816$01.50/0



I IV

Figure 1. Stereoelectronic effect in the extrusion of bromine in compounds of the type I and IV.

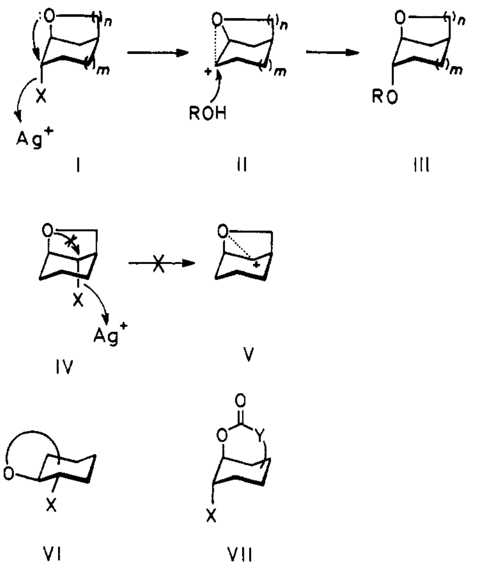
Chart I



of Ag$^+$. On the other hand, the role of the neighboring ether oxygen remained to be established.

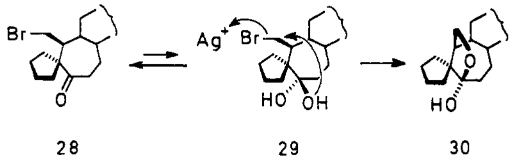
We tested a series of cyclic halo ethers, lactones, and carbonates prepared earlier in this laboratory[11] and found that while some of them underwent an instant reaction at room temperature, others were fairly stable even at elevated temperatures. Scheme II shows the successful cases: Halo ethers **2**, **3**, **9**, **11**, **13**, and **15** furnished corresponding hydroxy derivatives **6**, **10**, **12**, **14**, and **16**[12] with full retention of configuration when treated with $AgClO_4$ in aqueous 1,2-dimethoxyethane.[13,14] Analogously, alkoxy ethers **7** and/or **8** were formed in methanolic or ethanolic 1,2-dimethoxyethane, respectively. In contrast, halo epoxides **17**, **18**, **19**, and **20** remained unchanged and so did the halo lactones **21**, **22**, **23**, and cyclic carbonates **24**, **25**, and **26**. The phenylselenenyl derivative **27** was also inert (Chart I).

Scheme III[a]



[a] $m = 1, 2$; $n = 1, 2$.

Scheme IV



Discussion

It appears that the cyclic halo ethers can be divided topologically into two groups, depending on the location

---

(2) For review, see ref 1a and Capon, B.; McManus, S. P. *Neighboring Group Participation*; Plenum: New York, 1976; Vol. 1.

(3) (a) Kočovský, P.; Černý, V. *Collect. Czech. Chem. Commun.* **1978**, *43*, 327. For related examples see: (b) *Ibid.* **1978**, *43*, 1924. (c) *Ibid.* **1980**, *45*, 3030. (d) Kočovský, P.; Černý, V.; Synáčková, M. *Ibid* **1979**, *44*, 1483.

(4) (a) Woodward, R. B.; Brutcher, F. V. *J. Am. Chem. Soc.* **1958**, *80*, 209. (b) Henbest, H. B.; Smith, M. *J. Chem. Soc.* **1957**, 926. (c) Shopee, C. W.; Jones, D. N.; Summers, G. H. *J. Chem. Soc.* **1957**, 3100. (d) Wiberg, K. B.; Saegebarth, K. A. *J. Am. Chem. Soc.* **1957**, *79*, 6256. For a new modification of the Woodward–Prévost reaction that does not require the presence of silver(I), see the following: (e) Mangoni, L.; Adinolfi, M.; Barone, G.; Parrilli, M. *Tetrahedron Lett.* **1973**, 4485. (f) Parilli, M.; Barone, G.; Adinolfi, M.; Mangoni, L. *Gazz. Chim. Ital.* **1974**, *104*, 835.

(5) Kočovský, P.; Černý, V. *Collect. Czech. Chem. Commun.* **1978**, *43*, 327.

(6) Used either as commercially available substances or generated in situ from AcOAg and stoichiometric amounts of $HClO_4$ or CF_3COOH. No substantial difference in reactivity was observed.

(7) For the method, see: (a) Cambie, R. C.; Hayward, R. C.; Roberts, J. L.; Rutledge, P. S. *J. Chem. Soc., Chem. Commun.* **1973**, 359; *J. Chem. Soc., Perkin Trans. 1* **1974**, 1858. (b) Cambie, R. C.; Gash, D. M.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1157 and references cited therein. See also: (c) Cambie, R. C.; Hayward, R. C.; Jurlina, J. L.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2608. (d) Grieco, P. A.; Ivanga, J.; Sham, H. L.; Sasaki, S.; Kim, H. *J. Chem. Soc., Chem. Commun.* **1987**, 1044.

(8) Kočovský, P.; Pour, M., unpublished results.

(9) For other synthetically useful reactions that lead to formation of a single (or major) product, see, e.g.: (a) Greene, H. *C. R. Acad. Sci.* **1877**, *85*, 624. (b) Kasal, A. *Collect. Czech. Chem. Commun.* **1975** *40*, 140. (c) Kasal, A. *Ibid.* **1976**, *41*, 2040. (d) Hanson, J. R.; Reese, P. B.; Sadler, I. H. *Tetrahedron Lett.* **1982**, *23*, 1851. (d) Liu, H. J.; Browne, E. N. C.; Pednekar, P. R. *Can. J. Chem.* **1982**, *60*, 921. (e) Fetizon, M.; Golfier, M.; Montaufier, M. T.; Rens, J. *Tetrahedron* **1975**, *31*, 987.

(10) This effect can be anticipated to account for a number of transformations of organic halides that however, lead in most instances to complex mixtures of products with little selectivity. For examples, see: (a) Lemieux, R. U. *Can. J. Chem.* **1964**, *42*, 547. (b) Kasal, A. *Collect. Czech. Chem. Commun.* **1972**, *37*, 3095. (c) Kasal, A.; Trka, A. *Ibid.* **1974**, *38*, 603.

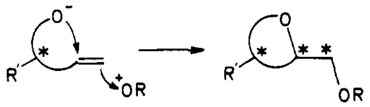
(11) For the preparation of the cyclic bromo ethers, see the following. (a) For **2**, ref 5. (b) For **9**, see: Kočovský, P. *Collect. Czech. Chem. Commun.* **1980**, *45*, 3008. (c) For **11** and **13**, see: Kočovský, P.; Kohout, L.; Černý, V. *Ibid.* **1980**, *45*, 559. (d) For **15**, see: Kočovský, P. *Ibid* **1983**, *48*, 3606. (e) For **17**, see Černý, V.; Kočovský, P. *Ibid* **1982**, *47*, 3062. (f) For **19**, see: Kočovský, P.; Černý, V. *Ibid* **1980**, *45*, 3030. For **20**, see: ref 11d. For **21** and **22**, see ref. 5. (g) For **23**, see: Kočovský, P.; Tureček, F. *Tetrahedron* **1983**, *39*, 3621. For **24** and **25**, see ref 3d. Synthesis of the iodo derivatives **3**, **18**, and **26** and the phenylselenenyl epoxide **27** will be published elsewhere (see ref 8).

(12) Alcohols were prepared earlier by an independent route from the corresponding epoxides by acid cleavage. (a) For **6**, see: Kočovský, P.; Černý, V. *Collect. Czech. Chem. Commun.* **1979**, *44*, 226. (b) For **10**, see: Kočovský, P.; Černý, V. *Ibid.* **1980**, *45*, 3199. For **12** and **14**, see ref 11c. The structure of **16** was inferred from its IR and ^{1}H NMR spectra.

(13) Numbers in parentheses represent isolated yields. According to the TLC and HPLC analyses of the crude reaction mixtures, all reactions gave products of >90% purity except for **11**, where a considerable amount of unidentified byproducts was formed.

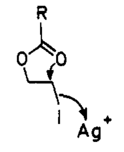
(14) All reactive bromo epoxides were converted to the hydroxy derivatives within several minutes except for **11** whose conversion took 3–4 h. This retardation can be attributed to the steric hindrance for coordination of silver(I) to the leaving bromine by the rest of the steroid skeleton.

Scheme V



of the halogen atom with respect to the oxygen bridge (Scheme III). Those having the structural feature as in the partial formula I (i.e., compounds **2**, **3**, **9**, **11**, **13**, and **15**) react smoothly,[14] while the remaining derivatives (**17**, **18**, and **19**) that contain the substructure IV are inert (Figure 1). Assuming the nucleophilic participation of the ether oxygen, we can see that in the former case this leads to the ion II, which is then trapped by the nucleophile in a stereospecific manner, giving III. On the other hand, in the latter instance (IV) the oxygen participation would lead to a highly strained ion V. Moreover, the oxygen lone pair in I overlaps nicely with the σ^* orbital of the C–X bond to be cleaved, whereas such an overlap is strongly impaired in IV (Figure 1). This behavior indicates that participation by the oxygen is a necessary condition for the reaction to occur and that special structural features have to be met. Furthermore, it turns out that the reaction is not confined to six-membered rings spanned by a five-membered ether bridge (as in **2**, **3**, **9**, and **11**), for both the bromo ethers **13** and **15** are readily converted to hydroxy derivatives **14** and **16**, respectively.

In all reactive halo ethers the mutual orientation of the leaving halogen and participating ether oxygen atoms was antiperiplanar. The compound **20** with gauche disposition is inert.[15] The lack of reactivity of halo lactones **21**–**23** and of carbonate **24** is probably a consequence of the decreased nucleophilicity of their ether oxygens and hence their ability to participate.[18] Thus, out of the substructures I, IV, VI, and VII listed in Scheme III, only the first one meets the fastidious structural requirements of this Koenigs–Knoor-type reaction. These findings clearly show that the pulling effect of the silver(I) ion and pushing ability of the antiperiplanar ether oxygen work together. This push–pull mechanism appears to be the driving force in Woodward–Prēvost reactions, where is promotes the extrusion of iodine (VIII).[19]



VIII

The transient ion II is highly oxophilic as it instantly reacts with oxygen nucleophiles. Attempts to introduce nitrogen and carbon nucleophiles were, thus far, unsuccessful.

The oxophilic character of the species arising by coordination of the silver(I) ion to bromine bonded to carbon can be further examplified by the smooth conversion of the known[20] bromo ketone **28** to the acetal **30** (Scheme IV). Although the bromo ketone **28** normally exists in its keto form as evidenced by the IR and ^{13}C NMR spectra,[20] silver(I) ions can selectively trap the hydrated species **29** populated in very minute concentration and produce the cyclic acetal **30**.[21]

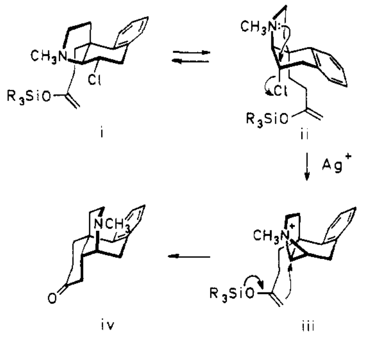
The synthetic value of our silver-assisted transformation is visualized in Scheme V. The overall process starting from an unsaturated alcohol and ending up with hydroxy or alkoxy ether can be formally considered as a one-pot electrophilic addition of RO$^+$ controlled by nucleophilic neighboring group participation. In principle, the cyclic hydroxy ether thus formed could also be prepared in two steps via epoxidation followed by acid cleavage of the epoxide.[22] However, the epoxidation of unsaturated alcohols is usually controlled by the OH group,[23] which gives rise to the *cis*-epoxy alcohols rather than the trans isomers requisit for this transformation. Furthermore, although alkyl ethers can be prepared by alkylation (RI/NaH) of the alcohols, these conditions are too harsh to allow for application of this method to sensitive polyfunctional molecules. Here, again, our mild and stereoselective method of umpolung may be of synthetic value.

Experimental Section

Materials and Equipment. Melting points (uncorrected) were obtained on a Kofler block. Optical rotations were measured in CHCl$_3$ with an error of ±3°. The infrared spectra were obtained on a Perkin-Elmer 621 instrument in CCl$_4$. ^{1}H NMR spectra were measured on Varian XL-200 (200.058 MHz, Ft mode) and Tesla BS 476 (60 MHz) instruments in CDCl$_3$ at 25 °C. Chemical shifts are given in δ values (ppm) relative to the signal of tetramethylsilane (δ = 0.00). Apparent coupling constants were obtained from the first-order analysis. The mass spectra were measured on a JEOL D-100 double focusing spectrometer (75 eV, 3 kV). The samples were introduced by using a direct inlet at lowest temperature enabling evaporation. The elemental com-

---

(15) An interesting example of nitrogen participation in extrusion of chlorine was published while this paper was in press (i → iv).[16] Although from the author's drawing it seems that gauche compound i is directly converted to the product iv, in view of our results it appears more likely that a conformational flipping to ii occurs prior the reaction. Such a conformational change should be energetically cheap in contrast to our rigid skeletons. As expected, the cis isomer of i is inert. For a detailed discussion of intramolecular nitrogen participation involving inversion of configuration at nitrogen, see ref 17a. For other related examples, see ref 17b,c.



(16) Borka, C. A.; Gertlis, J. F. *J. Org. Chem.* **1988**, *53*, 2144.

(17) (a) Heathcock, C. H.; von Gerden, T. W.; Lebrilla, C. B.; Maier, W. F. *J. Org. Chem.* **1985**, *50*, 968. (b) Dailey, C. D.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216. (c) Liu, H. L.; Browne, E. N. C.; Pendekar, P. R. *Can. J. Chem.* **1982**, *60*, 921.

(18) For comparison of the nucleophilicity of various neighboring groups, see: (a) Kočovský, P. *Collect. Czech. Chem. Commun.* **1983**, *48*, 3660. (b) Kočovský, P.; Stieborová, I. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1969.

(19) For discussion see ref 4. A similar effect in this reaction can be achieved by Cu(II) ions (ref 4e,f).

(20) Kočovský, P.; Tureček, F. *Collect. Czech. Chem. Commun.* **1981**, *46*, 2877 and 2892.

(21) For further examples of this behavior, see: Kato, M.; Kageyama, M.; Yoshikoshi, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1305.

(22) For another method employing Ce^{IV} oxidation of certain unsaturated alcohols, see: Fujise, Y.; Kobayashi, E.; Tsuchida, H.; Ito, S. *Heterocycles* **1978**, 351. Furthermore, a cis derivative can be prepared by a radical reaction, see: Kim, H.; Schlecht, M. F. *Tetrahedron Lett.* **1988**, *29*, 1771.

(23) (a) Henbest, A.; Wilson, R. A. *J. Chem. Soc.* **1957**, 1958. (b) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. For syn-directing effects of other groups in epoxidation, see: (c) Kočovský, P. *Tetrahedron Lett.* **1986**, *27*, 5521. (d) Kočovský, P. *Ibid.* **1988**, *29*, 2475. (e) For review, see ref 1a.

J. Org. Chem. 1988, 53, 5819–5825

position of ions was determined by accurate mass measurements. Standard workup of an ethereal solution means washing with 5% HCl (aqueous), water, and 5% $KHCO_3$ (aqueous), drying with Na_2SO_4, and evaporation of the solvent in vacuo. Light petroleum ether refers to the fraction boiling in the range 40–60 °C. The identity of samples prepared by different routes was checked by mixed melting point determination, TLC, and IR and NMR spectra. Yields are given in milligrams of isolated product showing one spot on a chromatographic plate and no trace of impurities detectable in the NMR spectrum.

General Procedure for the Silver-Assisted Substitution. To a stirred solution of the cyclic halo ether (0.25 mmol) in 1,2-dimethoxyethane (5 mL) containing water (0.5 mL) or alcohol (0.5 mL) was added at room temperature a solution of silver trifluoroacetate or perchlorate (0.30 mmol) in 1,2-dimethoxyethane (1 mL) over 1 min. An instant formation of a yellowish sediment of silver halogenide was observed. The mixture was stirred at room temperature for another 5 min, the insoluble material was filtered off and washed with ether, and the filtrate was diluted with water and worked up. The product was dissolved in benzene or in a benzene–ether (5:1) mixture and filtered through a pad of aluminum oxide and the solvent was evaporated in vacuo. In cases when this procedure still did not give a pure product (**7**, **8**, **12**, and **16**), the residue was chromatographed on two plates of silica gel (20 × 20 cm) with a light petroleum ether–ether–acetone (70:15:15) mixture as developer to obtain pure hydroxy derivatives. The isolated yields are given in Scheme II.

General Procedure for the Silver-Assisted Addition. A solution of iodine (0.30 mmol) in 1,2-dimethoxyethane or dioxane (1 mL) was added to a solution of unsaturated alcohol (0.25 mmol) in 1,2-dimethoxyethane or dioxane (5 mL) containing water or methanol (0.5 mL) and silver trifluoroacetate (0.30 mmol) at room temperature over 1 min. Immediate formation of yellowish silver iodide was observed. The mixture was stirred for another 5 min, and the solid material was filtered off and washed with ether. The filtrate was washed with water, 5% $Na_2S_2O_3$ (aqueous), 5% $KHCO_3$ (aqueous), and water and dried with Na_2SO_4, and the solvent was evaporated in vacuo. The residue was dissolved in a benzene–ether mixture (5:1) and filtered through a pad of aluminum oxide, and the filtrate was evaporated to afford pure products. The isolated yields are given in the text. According to the TLC analysis of the crude reaction mixtures, all products were of >90% purity.

2β,19-Epoxy-5α-cholestan-3α-ol (6): mp 191–193 °C; $[\alpha]^{20}_{D}$ +33° (*c* 2.0) [authentic sample[12a] mp 190–192 °C; $[\alpha]^{20}_{D}$ +35°].

2β,19-Epoxy-3α-methoxy-5α-cholestane (7): $[\alpha]^{20}_{D}$ +36° (*c* 4.2); IR 1062, 1097 cm^{-1}; ^{1}H NMR 0.58 (s, 3 H, 18-H), 3.30 (s, 3 H, MeO), 3.62 and 3.73 (AB system, J = 7 Hz, 2 H, 19-H), 3.87 (m, W = 12 Hz, 1 H, 3β-H), 4.25 (dd, J = 5.5 and 4.5 Hz, 1 H, 2α-H).

Anal. Calcd for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.36; H, 11.94.

2β,19-Epoxy-3α-ethoxy-5α-cholestane (8): mp 80–82 °C; $[\alpha]^{20}_{D}$ +33° (*c* 1.8); ^{1}H NMR 0.62 (s, 3 H, 18-H), 1.18 (t, J = 7 Hz, 3 H, CH_3CH_2O), 3.47 (q, J = 7 Hz, 2 H, CH_3CH_2O), 3.64 and 3.77 (AB system, J = 8.5 Hz, 2 H, 19-H), 3.93 (ddd, J = 9, 8, and 2.5 Hz, 1 H, 3β-H), 4.23 (dd, J = 6 and 5 Hz, 1 H, 2α-H).

Anal. Calcd for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 80.49; H, 12.03.

4β,19-Epoxy-5α-cholestan-3α-ol (10): mp 174–175 °C; $[\alpha]^{20}_{D}$ +44° (*c* 2.0) [authentic sample[12b] mp 175–176 °C; $[\alpha]^{20}_{D}$ +42°].

6β,19-Epoxy-5α-cholestane-3β,7α-diol 3-monoacetate (12): mp 159–160 °C; $[\alpha]^{20}_{D}$ −19° (*c* 2.0) [authentic sample[11c] mp 158–159 °C; $[\alpha]^{20}_{D}$ −22°].

6β,19-Epoxy-*B*-homo-5α-cholestane-3β,7α-diol 3-monoacetate (14): mp 185–187 °C; $[\alpha]^{20}_{D}$ −6° (*c* 2.2) [authentic sample[11c] mp 184–186 °C; $[\alpha]^{20}_{D}$ −8°].

2β,19a-Epoxy-19-homo-5α-cholestan-3α-ol (16): mp 152–154 °C (aqueous acetone); $[\alpha]^{20}_{D}$ +23° (*c* 1.9); ^{1}H NMR 0.63 (s, 3 H, 18-H), 3.82 (m, W = 25 Hz, 4 H).

Anal. Calcd for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found C, 80.43; H, 11.85.

Acetal 30. To a solution of bromo ketone **28**[20] (100 mg) in a mixture of 1,2-dimethoxyethane (4 mL) and water (0.2 mL) was added solid silver perchlorate (200 mg). The mixture was stirred at room temperature overnight and then worked up as given in the general procedure to furnish the acetal **30** (76 mg): mp 147–149 °C (aqueous acetone); IR 3400, 3615 cm^{-1}; ^{1}H NMR 0.70 (s, 3 H, 18-H), 3.59 (br d, J_{gem} = 8.4 Hz, 1 H, 19-H) 4.28 (dd, J_{gem} = 8.4 Hz, J = 7.1 Hz, 1 H, 19-H); ^{13}C NMR 12.69 (q), 18.58 (q), 22.53 (q), 22.79 (q), 23.80 (t), 24.44 (t), 24.90 (t), 25.97 (t), 26.48 (t), 27.98 (d), 28.22 (t), 29.35 (t), 32.97 (t), 35.78 (d), 36.07 (t), 38.05 (t), 39.15 (d), 39.48 (t), 40.94 (t), 43.42 (s), 52.84 (d), 54.62 (d), 55.92 (s), 56.26 (d), 56.74 (d), 76.51 (t), 108.58 (s).

Acknowledgment. We thank Dr. S. Vašíčková for measurement and interpretation of IR spectra, Dr. J. Zajíček, J. Jelínková, and M. Snopková for measurement of ^{1}H NMR spectra, Dr. V. Hanuš for measurement and interpretation of mass spectra, and the staff of the Analytical Laboratory of this Institute (Head Dr. V. Pechanec) for elemental analyses.

Registry No. **1**, 28809-51-0; **2**, 66452-55-9; **3**, 116910-89-5; **6**, 27559-16-6; **7**, 71789-07-6; **8**, 116910-90-8; **9**, 77050-56-7; **10**, 77733-02-9; **11**, 74027-09-1; **12**, 74027-10-4; **13**, 74703-68-7; **14**, 74027-12-6; **15**, 90360-76-2; **16**, 116910-91-9; **17**, 28790-39-8; **18**, 116910-92-0; **19**, 77733-01-8; **20**, 116910-93-1; **21**, 66452-57-1; **22**, 66452-59-3; **23**, 89327-93-5; **24**, 115041-17-3; **25**, 71781-20-9; **26**, 116910-94-2; **27**, 116910-95-3; **28**, 79876-06-5; **30**, 116925-98-5.

Enhancement of the Resonance Interaction of Out-of-Plane Methoxy Groups by Ortho Substituents in Crowded Anisoles

Ingeborg I. Schuster,* Masood Parvez, and Alan J. Freyer

Department of Chemistry, The Pennsylvania State University, The Ogontz Campus,
Abington, Pennsylvania 19001

Received June 20, 1988

The ^{17}O and ^{13}C NMR chemical shifts of substituted anisoles provide evidence that the resonance interaction of methoxy groups which are perpendicular to the aromatic ring in crowded anisoles is influenced, to varying degrees, by ortho substituents. Enhancement of methoxy-to-aryl electron delocalization, brought about by these groups, follows the order isopropyl < ethyl < methyl ≪ methoxy (in-plane) < *tert*-butyl. By an analysis of the molecular structures of several 3,5-dialkylanisic acids, related to 2,6-dialkylanisoles, this order becomes explicable in terms of repulsions between the lone pair electrons of the methoxy oxygen and bonding electrons of the proximate substituents. Methoxy groups that lie in the molecular plane are not similarly affected by neighboring substituents.

According to recent ab initio MO calculations[1] and X-ray analyses[2] the methoxy groups of sterically unhindered anisoles tend to lie in the aromatic plane, with an Ar–O–Me bond angle of 117–118°, a value near that expected for

0022-3263/88/1953-5819$01.50/0