Each of these reactions was very clean, producing a single enol silyl ether which could be purified by simple distillation. Furthermore, the products **18** and **20** were quite stable and, with reasonable precautions (e.g., exclusion of air), these compounds have been stored at <0 °C without change for fairly long periods of time (e.g., >2 months for **20**).

Transmetalation of compounds **18** and **20** was accomplished by treatment (THF, −78 °C, 1–1.5 h) of these substances with 1.1 equiv of methyllithium and *n*-butyllithium, respectively. Protonation (HOAc) of the resultant vinyllithium intermediate **21** afforded (84% from **18**, 87% from **20**) 2-(*tert*-butyldimethylsiloxy)-1,3-cyclohexadiene (**22**). More importantly, the intermediate **21** also reacted smoothly with a variety of other electrophilic reagents to produce the corresponding substituted 1,3-cyclohexadienes. Some of the results we have obtained are summarized in Table I.

In connection with the data tabulated in Table I, the following points should be noted. (a) Although the reaction of the lithio derivative **21** with carbonyl compounds proceeded to completion at −78 °C (~1 h), the alkylation reactions were carried out for 1 h at −78 °C and 1 h at room temperature. (b) In general, each of the products could be purified by means of a simple distillation. Of the two precursors (**18**, **20**) of the lithio intermediate **21**, the use of **18** was somewhat more convenient, since the relatively volatile tetramethyltin could be separated very easily from the various products **23**. (c) Hydrolysis (1 N hydrochloric acid in THF, room temperature) of the enol silyl ether functionality of the products **23** proceeded without incident, producing the corresponding β-substituted enones in good yield.

A typical experimental procedure follows. To a cold (−78 °C), stirred solution of **18** (100 mg) in 5 mL of dry THF, under an atmosphere of argon, was added dropwise a solution of methyllithium in ether (0.23 mL, 1.28 M), and the resultant yellow solution was stirred at −78 °C for 1 h. Cyclohexanone (34 mg) was added and the reaction mixture was stirred for an additional period of 1 h. After successive addition of saturated aqueous sodium bicarbonate (~0.2 mL) and ether (30 mL), the mixture was allowed to warm to room temperature. The crude product (isolated with ether) was distilled [air-bath temperature 127–135 °C (0.07 Torr)], affording 76 mg (92%) of compound **23** (E = 1-hydroxycyclohexyl): UV λ_{max} (MeOH) 268 nm (ϵ 5250); IR (film) 3420, 1653, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6 H), 0.88 (s, 9 H), 1.22 (s, 1 H, exchanged with D_2O), 1.48–1.64 (broad unresolved signal, 10 H), 2.08–2.14 (m, 4 H), 4.82 (m, 1 H, $W_{1/2}$ = 8 Hz), 5.74 (m, 1 H, $W_{1/2}$ = 4 Hz); exact mass calcd for $C_{18}H_{32}O_2Si$ 308.2171, found 308.2174.

Work in this area is continuing.

Acknowledgment. Financial support from the National Sciences and Engineering Research Council Canada (NSERC) and a NSERC postgraduate scholarship (to H.E.M.) are gratefully acknowledged.

Registry No. **17**, 69519-95-5; **18**, 71106-30-4; **19**, 71106-31-5; **20**, 71106-32-6; **21**, 71106-33-7; **22**, 71106-34-8; **23** (E = CH_3), 71106-35-9; **23** (E = $CH_3(CH_2)_3$), 71106-36-0; **23** (E = 2-cyclopentenyl-$(CH_2)_2$), 71106-37-1; **23** (E = $Br(CH_2)_4$), 71106-38-2; **23** (E = $Cl(CH_2)_4$), 71106-39-3; **23** (E = 1-hydroxycyclohexyl), 71129-42-5; **23** (E = 1-hydroxycyclopentyl), 71106-40-6; **23** (E = 1-hydroxy-2-cyclohexenyl), 71106-41-7; **23** (E = $C_6H_5CH(OH)$), 71106-42-8; CH_3I, 74-88-4; $CH_3(CH_2)_3Br$, 109-65-9; 2-cyclopentenyl$(CH_2)_2Br$, 21297-99-4; $Cl(CH_2)_4Br$, 6940-78-9; cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; 2-cyclohexen-1-one, 930-68-7; C_6H_5CHO, 100-52-7.

(11) Prepared by reaction of **11** with lithium phenylthio(tri-*n*-butylstannyl)cuprate (cf. ref 9).

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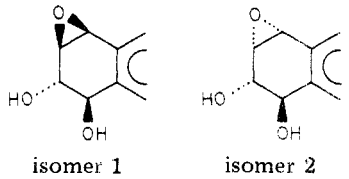
Benzo-Ring Diol Epoxides of Benzo[*e*]pyrene and Triphenylene

Summary: Synthesis and isolation of the first examples of conformationally rigid, diastereomeric pairs of diol epoxides from *trans*-dihydrodiols are described. Direct epoxidation of the bay-region benzo[*e*]pyrene 9,10-dihydrodiol and triphenylene 1,2-dihydrodiol produces ca. 1:1 mixtures of diastereomeric diol epoxides in which the benzylic hydroxyl group is either cis (isomer **1**) or trans (isomer **2**) to the epoxide oxygen. Relative stereochemistry is assigned through spectral methods, solvolysis to tetraols, and an alternate route of synthesis.

Sir: The bay-region theory[1] predicted that benzo-ring diol epoxides of polycyclic aromatic hydrocarbons, in which the epoxide group forms part of a bay region, should be among the chemically most reactive and presumably most biologically active metabolites of a given hydrocarbon. Evidence has been forthcoming which indicates that this is indeed the case for the eight hydrocarbons which have since been adequately studied.[2] For diol epoxides of benzo-ring *trans*-dihydrodiols, two diastereomers are possible in which the benzylic hydroxyl group is either cis (isomer **1**) or trans (isomer **2**) to the epoxide oxygen. In



isomer 1 isomer 2

the absence of conformational restraints imposed by a proximate bay region, the hydroxyl groups of non-bay-region dihydrodiols reside in a predominantly quasi-diequatorial conformation, as evidenced by the large values of J_{diol} in their ^{1}H NMR spectra.[3] As described in detail elsewhere,[4] the allylic quasi-equatorial hydroxyl group acts

(1) The simplest example of a bay region is the hindered area between the 4 and 5 positions in phenanthrene. For details of the theory see: D. M. Jerina and J. W. Daly in "Drug Metabolism", D. V. Parke and R. L. Smith, Eds., Taylor and Frances, London, 1976, pp 13–32; D. M. Jerina, R. E. Lehr, H. Yagi, O. Hernandez, P. G. Wislocki, A. W. Wood, R. L. Chang, W. Levin, and A. H. Conney in "In Vitro Metabolic Activation in Mutagenesis Testing", F. J. DeSerres, J. R. Fouts, J. R. Bend, and R. M. Philpot, Eds., Elsevier/North Holland Biomedical Press, Amsterdam, 1976, pp 159–177; D. M. Jerina and R. E. Lehr in "Microsomes and Drug Oxidations", V. Ullrich, I. Roots, A. G. Hildebrant, R. W. Estabrook, and A. H. Conney, Eds., Pergamon Press, Oxford, England, 1977. pp 709–720.

(2) For leading references see D. R. Thakker, M. Nordqvist, H. Yagi, W. Levin, D. Ryan, P. Thomas, A. J. Conney, and D. M. Jerina in "Polynuclear Aromatic Hydrocarbons", P. W. Jones and P. Leber, Eds., Ann Arbor Science Publishers, Ann Arbor, Michigan, 1979, pp 455–472; M. K. Buening, W. Levin, A. W. Wood, R. L. Chang, H. Yagi, J. M. Karle, D. M. Jerina, and A. H. Conney, *Cancer Res.*, **39**, 1310 (1979).

(3) D. M. Jerina, H. Selander, H. Yagi, M. C. Wells, J. F. Davey, V. Mahadevan, and D. T. Gibson, *J. Am. Chem. Soc.*, **98**, 5988 (1976); D. T. Gibson, V. Mahadevan, D. M. Jerina, H. Yagi, and H. J. C. Yeh, *Science*, **189**, 295 (1975); R. Lehr, M. Schaefer-Ridder, and D. M. Jerina, *J. Org. Chem.*, **42**, 736 (1977); J. M. Karle, H. D. Mah, D. M. Jerina and H. Yagi, *Tetrahedron Lett.*, 4021 (1977).

Table I. ^{1}H NMR Spectra (100 MHz, acetone-d_6) of the Pairs of Diol Epoxides Derived from Benzo[*e*]pyrene 9,10-Dihydrodiol and Triphenylene 1,2-Dihydrodiol

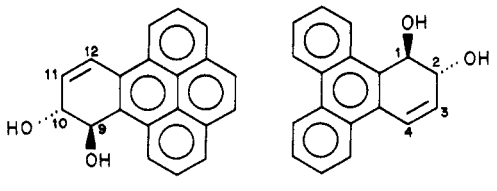
compd[a]	benzylic carbinol	nonbenzylic carbinol	benzylic epoxide	nonbenzylic epoxide
benzo[*e*]pyrene 9,10-diol 11,12-epoxide[b]				
isomer 1	H_9 5.56	H_{10} 4.79	H_{12} 5.24	H_{11} 4.16
(mp 213-214 °C)		($J_{9,10}$ = 2.5, $J_{10,11}$ = 3.0, $J_{11,12}$ = 4.5, $J_{9,11}$ = 2.5)		
isomer 2	H_9 5.41	H_{10} 4.56	H_{12} 4.82	H_{11} 4.15
(mp 160 °C)		($J_{9,10}$ = 3.5, $J_{10,11}$ = 5.0, $J_{11,12}$ = 4.0)		
triphenylene 1,2-diol 3,4-epoxide[c]				
isomer 1	H_1 5.37	H_2 4.69	H_4 5.09	H_3 4.10
(mp 184-186 °C)		($J_{1,2}$ = $J_{1,3}$ = $J_{2,3}$ = 1.7, $J_{3,4}$ = 4.2)		
isomer 2	H_1 5.26	H_2 4.50	H_4 4.63	H_3 4.09
(mp 155-156 °C)		($J_{1,2}$ = 3.5, $J_{2,3}$ = 5.0, $J_{3,4}$ = 4.2)		

[a] Spectra were recorded both before and after (reported values) addition of CD_3OD. Chemical shifts (δ) are in ppm relative to Me_4Si and coupling constants (J) are in hertz. [b] See note 10. [c] See note 11.

to direct epoxidation via peroxy acid to the same face of the dihydrodiol as the nonbenzylic hydroxyl group (isomer **2**). Since *N*-bromoacetamide also attacks the same face of the dihydrodiol, the resultant bromo triol can be dehydrohalogenated to the isomer **1** diol epoxide.[4] The very high stereoselectivity of these two reactions has been confirmed by other laboratories.[5] The above conclusions regarding the stereoselective attack of either peroxy acid or *N*-bromoacetamide apply regardless of whether or not the double bond of the dihydrodiol forms part of a bay region of the hydrocarbon.

Two additional stereochemical possibilities exist: either the diol group only or the diol group as well as the double bond can form parts of bay regions of the hydrocarbon. When the diol group forms part of a bay region, such as is the case for benzo[*a*]anthracene 1,2-dihydrodiol and benzo[*a*]pyrene 9,10-dihydrodiol, the *trans*-hydroxyl groups reside in a predominantly quasi-diaxial conformation due to steric hindrance at the bay region.[3] In both cases, the key nonbenzylic hydroxyl group should not exert a strong directing influence on the stereoselectivity of attack by peroxy acid[6] due to its quasi-axial conformation.[3] Thus peroxy acid produces mixtures of isomer **1** and **2** diol epoxides in each case.[7]

The present study examines the stereochemical situation where both the diol group and the double bond form parts of bay regions of the hydrocarbon: epoxidation of benzo[*e*]pyrene 9,10-dihydrodiol and triphenylene 1,2-dihydrodiol. Despite our recent report[8] that direct epoxidation of the benzo[*e*]pyrene 9,10-dihydrodiol produced a mixture of products in accord with our expectations,[4,7] Harvey et al.[9] have claimed that both benzo[*e*]pyrene 9,10-dihydrodiol and triphenylene 1,2-dihydrodiol are cleanly converted into diol epoxides of the isomer **2** series in 79 and 60% yields, respectively.



benzo[*e*]pyrene-9,10-dihydrodiol triphenylene-1,2-dihydrodiol

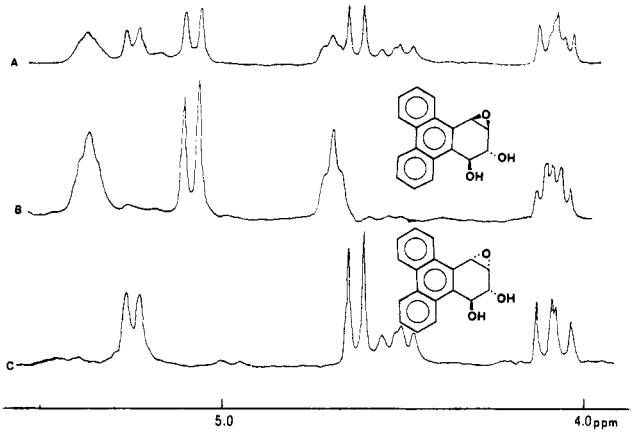


Figure 1. ^{1}H NMR spectra (100 MHz, acetone-d_6) of (A) crude epoxidation products from triphenylene 1,2-dihydrodiol, (B) less polar 1,2-diol 3,4-epoxide **1** isolated from above, and (C) more polar 1,2-diol 3,4-epoxide **2** isolated from above. Spectra are shown after treatment of the samples with CD_3OD.

Epoxidation (500 mg of *m*-chloroperoxybenzoic acid in 2.5 mL of THF) of benzo[*e*]pyrene 9,10-dihydrodiol (10 mg) for 40 min at room temperature resulted in nearly quantitative formation of two new compounds in equal amounts as judged by LC.[10] Similar epoxidation of triphenylene 1,2-dihydrodiol[11] also clearly produced two products in nearly equal amounts (ratio 56:44). A major breakthrough in studying these products has been our finding that diol epoxides, including the highly reactive 7,8-diol 9,10-epoxides of benzo[*a*]pyrene, can be chro-

(4) H. Yagi, O. Hernandez, and D. M. Jerina, *J. Am. Chem. Soc.*, **97**, 6881 (1975); H. Yagi, D. R. Thakker, O. Hernandez, M. Koreeda, and D. M. Jerina, *ibid.*, **99**, 1604 (1977); R. E. Lehr, M. Schaefer-Ridder, and D. M. Jerina, *Tetrahedron Lett.*, 539 (1977); D. L. Whalen, A. M. Ross, H. Yagi, J. M. Karle, and D. M. Jerina, *J. Am. Chem. Soc.*, 5218 (1978).

(5) D. J. McCaustland, D. L. Fischer, W. P. Duncan, E. J. Ogilvie, and J. F. Engel, *J. Labeled Compd. Radiopharm.*, **12**, 583 (1976); F. A. Beland and R. G. Harvey, *J. Chem. Soc., Chem. Commun.*, 84 (1976).

(6) H. B. Henbest, *Proc. Chem. Soc. London*, 159 (1963); T. Itoh, K. Jitsukawa, K. Kaneda, and S. Teranishi, *J. Am. Chem. Soc.*, **101**, 159 (1979).

(7) A. W. Wood, R. L. Chang, W. Levin, R. E. Lehr, M. Schaefer-Ridder, J. M. Karle, D. M. Jerina, and A. H. Cooney, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 2746 (1977); D. R. Thakker, H. Yagi, R. E. Lehr, W. Levin, A. Y. H. Lu, R. L. Chang, A. W. Wood, A. H. Conney, and D. M. Jerina, *Mol. Pharmacol.* **14**, 502 (1978).

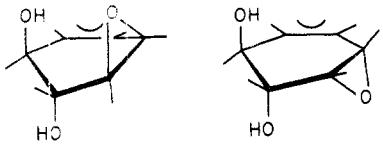
(8) R. E. Lehr, C. W. Taylor, S. Kumar, H. D. Mah, and D. M. Jerina, *J. Org. Chem.*, **43**, 3462 (1978).

(9) R. G. Harvey, H. M. Lee, and N. Shyamasundar, *J. Org. Chem.*, **44**, 78 (1979).

(10) Workup consisted of addition of ether and aqueous 10% NaOH. The organic phase was dried and concentrated. LC on a DuPont Zorbax SIL column (0.62 × 25 cm) eluted with 40% THF in hexane indicated the presence of two products in the ratio of 49:51 based on absorbance at 254 nm; k' = 4.4 for diol epoxide **1** and k' = 6.0 for diol epoxide **2** as described in detail later. These and all other compounds in this study had the required molecular ions in their chemical ionization (NO–N_2) mass spectra.

(11) Only 100 mg of *m*-chloroperoxybenzoic acid in 2.0 mL of THF was used, and the reaction was terminated at 1 h. The ratio of the two products on LC was 56:44 based on absorbance at 254 nm with 30% THF in hexane as eluent; k' = 3.1 for diol epoxide **1** and k' = 4.2 for diol epoxide **2** (minor product), respectively.

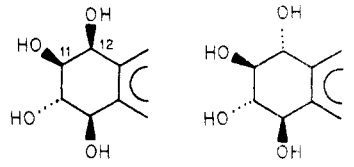
matographed on LC with THF/hexane based solvent systems. The two products from each of the above epoxidations were purified by separation on LC. The ^1H NMR spectra of the mixture as well as the separated oxidation products from triphenylene 1,2-dihydrodiol are presented in Figure 1 and the ^1H NMR spectra of all four diol epoxides are recorded in Table I. Consideration of conformational factors alone should allow assignment of relative stereochemistry (isomer **1** or **2**) to the members of each pair of diol epoxides. Due to steric crowding in the bay region,[3] the hydroxyl groups must exist in a predominantly quasi-diaxial conformation as shown below.[12]



isomer 1 isomer 2

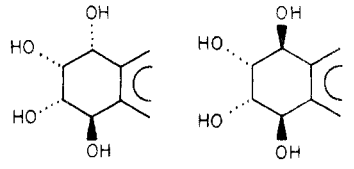
This is evident from the very small values of J_{diol} = 1.7–3.5 Hz for the trans diols in all four molecules (Figure 1 and Table I). Two additional unique consequences arise because of these relatively fixed conformations: (i) the benzylic carbinol C–H bond and the nonbenzylic oxirane C–H bond are nearly coplanar in the isomer **1** series such that a ^4J "W" coupling[13] should be detectable; and (ii) the plane of the epoxide ring in the isomer **2** series must be nearly perpendicular to the plane of the π-electron system such that its benzylic oxirane hydrogen is tilted away from the edge of the aromatic nucleus, thereby suffering less "edge deshielding"[14] relative to this hydrogen in the isomer **1** series. Thus, the presence of $J_{9,11}$ = 2.5 Hz (benzo[*e*]pyrene) and $J_{1,3}$ = 1.7 Hz (triphenylene) along with the fact that the benzylic oxirane hydrogens are at 0.42–0.46 ppm lower field argues strongly in favor of these being diol epoxide **1** isomers from the two hydrocarbons.[15]

In order to further substantiate our assignments of relative stereochemistry, we have hydrolyzed the benzo[*e*]pyrene diol epoxide isomers **1** and **2** to mixtures of tetraols by cis and trans addition of water at C-12 as shown. Because of the unique symmetry properties of *trans*-**1** and *trans*-**2**, their ^1H NMR spectra as their tetraacetates should be quite diagnostic. The tetraacetate of *trans*-**1** should have all of the acetate groups quasi-axial with $J_{9,10} = J_{11,12} \sim 2$ Hz. This isomer was obtained from benzo[*e*]pyrene diol epoxide **1**; $H_{9,12}$ δ 6.91 and $H_{10,11}$ δ 5.61 as apparent triplets with J = 1.6 Hz. The tetraacetate of *trans*-**2** obtained from benzo[*e*]pyrene diol epoxide **2** gave the expected pair of doublets: $H_{9,12}$ δ 6.97 and $H_{10,11}$ δ 5.84



cis-**1** *trans*-**1**

from benzo[*e*]pyrene diol epoxide **1**

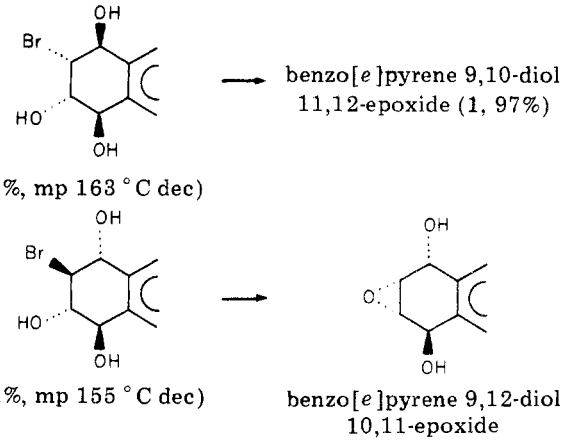


cis-**2** *trans*-**2**

from benzo[*e*]pyrene diol epoxide **2**

with $J_{9,10} = J_{11,12}$ = 4.5 Hz. Complete details of the hydrolysis of all four diol epoxides, purification of the resulting tetraols, and ^1H NMR spectra of their tetraacetates are given in the Supplementary Material.

Further evidence in support of the structures assigned to the benzo[*e*]pyrene diol epoxides came from the reaction of benzo[*e*]pyrene 9,10-dihydrodiol with *N*-bromoacetamide to form a pair of bromo triols and their subsequent dehydrobrominations. Treatment of the major bromo triol (71%) with the hydroxide form of Amberlite resin produced only the benzo[*e*]pyrene 9,12-diol 10,11-epoxide.



(29%, mp 163 °C dec) benzo[*e*]pyrene 9,10-diol 11,12-epoxide (1, 97%)

(71%, mp 155 °C dec) benzo[*e*]pyrene 9,12-diol 10,11-epoxide

Since only the bromo triol shown could give benzo[*e*]pyrene 9,12-diol 10,11-epoxide, the structures of both bromo triols are established. The base treatment of the minor bromo triol (29%) under the same condition gave the expected diol epoxide **1**. The assignments of the benzo[*e*]pyrene 9,10-diol 11,12-epoxides are thus confirmed. Synthetic and spectral details are presented with the Supplementary Material.

The present report describes the first synthesis of bay-region diol epoxides of polycyclic hydrocarbons in which the molecules are conformationally rigid. Previous stereoelectronic considerations by Whalen et al.[4] suggested that diol epoxides were most reactive when the plane of the oxirane ring was perpendicular to the π-electron system. The diol epoxide **2** isomers in this study are locked in this conformation, whereas the diol epoxide **1** isomers are locked out of this conformation.

Preliminary solvolysis data on the pair of benzo[*e*]pyrene diol epoxides suggest that isomer **2** is indeed more reactive under neutral conditions. Interestingly, both benzo[*e*]pyrene diol epoxides are only weakly mutagenic toward *S. typhimurium* strains TA98 and TA100, while 9,10-epoxy-7,8,9,10-tetrahydrobenzo[*e*]pyrene is highly mutagenic,[16] a result which suggests that the axial hydroxyl

(12) The conformation shown is that which is generally preferred for the isomer **1** series despite adverse interactions between the benzylic oxirane hydrogen and the proximate aromatic hydrogen when the epoxide forms part of a bay region. Thus, for non-bay-region diol epoxides such as naphthalene 1,2-diol 3,4-epoxide **1**[4] and benzo[*a*]anthracene 8,9-diol 10,11-epoxide **1** or 10,11-diol 8,9-epoxide 1,[4] the values of J_{diol} are significantly smaller (more diaxial hydroxyl groups) than they are for diol epoxides in which the epoxide forms part of a bay region such as benzo[*a*]pyrene 7,8-diol 9,10-epoxide **1**.

(13) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964); M. Barfield, *J. Chem. Phys.*, **41**, 3825 (1964).

(14) K. D. Bartle and D. W. Jones, *Adv. Org. Chem.*, **8**, 317 (1972).

(15) The ^1H NMR spectrum of the diol epoxide from benzo[*e*]pyrene 9,10-dihydrodiol reported by Harvey et al.[9] more closely resembles that of isomer **1** rather than isomer **2**, which was the structure claimed by those authors. Since the ratio of the isomer **1** to **2** diol epoxides was always 1:1 under a variety of oxidation conditions, either the reported yield of 79% for a single pure isomer[9] or the isomeric purity is questionable. The ^1H NMR spectrum which they report for the oxidation products from the triphenylene 1,2-dihydrodiol is that of the mixture of both diol epoxides isomers (**1** and **2**) with the exception that the highest field signal was not described.

groups and/or the rigid conformations may be detrimental to high biological activity.

Registry No. Benzo[*e*]pyrene diol epoxide **1**, 70981-75-8; benzo[*e*]pyrene diol epoxide **2**, 68151-05-3; triphenylene diol epoxide **1**, 70981-76-9; triphenylene diol epoxide **2**, 68151-06-4; *trans*-**1** benzo[*e*]pyrene tetraol, 70940-90-8; *cis*-**1** benzo[*e*]pyrene tetraol, 70981-77-0; *trans*-**2** benzo[*e*]pyrene tetraol, 70981-78-1; *cis*-**2** benzo[*e*]pyrene tetraol, 70981-79-2; *trans*-**1** triphenylene tetraol, 70940-91-9; *trans*-**2** triphenylene tetraol, 70981-80-5; *cis*-**2** triphenylene tetraol, 70981-81-6; benzo[*e*]pyrene 11-bromo-9,10,12-triol, major isomer, 70940-92-0; benzo[*e*]pyrene 11-bromo-9,10,12-triol, minor isomer, 70981-82-7; 10,11-epoxy-9,12-dihydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene, 70940-93-1; 10,11-epoxy-9,12-dihydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene diacetate, 70982-62-6; *trans*-**1** triphenylene tetraol tetraacetate, 70940-94-2; *trans*-**2** triphenylene tetraol tetraacetate, 70981-83-8; *cis*-**2** triphenylene tetraol tetraacetate, 70981-84-9; *trans*-**1** benzo[*e*]pyrene tetraol tetraacetate, 70940-95-3; *cis*-**1** benzo[*e*]pyrene tetraol tetraacetate, 70981-85-0; *trans*-**2** benzo[*e*]pyrene tetraol tetraacetate, 70981-86-1; *cis*-**2** benzo[*e*]pyrene tetraol tetraacetate, 70981-87-2.

Supplementary Material Available: Details on the hydrolysis of the benzo[*e*]pyrene and triphenylene diol epoxides to tetraols and their ^{1}H NMR spectra as tetraacetates, and the reaction of benzo[*e*]pyrene 9,10-dihydrodiol with *N*-bromoacetamide as well as the cyclization of the resultant bromo triols (4 pages). Ordering information is given on any current masthead page.

(16) A. W. Wood, W. Levin, D. R. Thakker, H. Yagi, R. L. Chang, D. E. Ryan, P. E. Thomas, P. M. Dansette, N. Whittaker, S. Turujman, R, E. Lehr, S. Kumar, D. M. Jerina, and A. H. Cooney, *J. Biol. Chem.*, **254**, 4408 (1979), and unpublished results of A. W. Wood.

(17) This investigation was supported, in part, by Grant No. 1 R01 Ca-22985-02, awarded to R.E.L. at the Department of Chemistry, University of Oklahoma, by the National Cancer Institute, DHEW.

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Removal of Benzyl-type Protecting Groups from Peptides by Catalytic Transfer Hydrogenation with Formic Acid

Summary: Formic acid is shown to be a particularly effective hydrogen donor for the rapid removal of peptide benzyl and benzyloxycarbonyl protecting groups by catalytic transfer hydrogenation.

Sir: Catalytic transfer hydrogenation has been shown to be a useful procedure for the removal of benzyl and benzyloxycarbonyl protecting groups in peptide synthesis.[1-4] Good yields of deprotected products have been obtained under relatively mild conditions using both cyclohexene and 1,4-cyclohexadiene as hydrogen donors. Transfer hydrogenation appears to be preferable in several respects to catalytic hydrogenation,[1-4] but has its own shortcomings. Probably the most important of these is the immiscibility of most peptides or peptide derivatives with the apolar hydrogen donors and/or their dehydrogenation product, benzene. The present work describes the use of formic acid, a good solvent for most peptides, as a convenient hydrogen donor for catalytic transfer hydrogenation.[5]

Results and Discussion

A large number of hydrogen donors have been used for catalytic transfer hydrogenation but cyclohexene has generally been preferred.[6] Rates of hydrogen transfer, however, vary considerably with different donors and the use of 1,4-cyclohexadiene, for example, greatly facilitates the deprotection of peptide benzyl and benzyloxycarbonyl derivatives and allows for more rapid deprotection at lower temperatures.[4] Formic acid, by the same criteria, appears to be a particularly facile hydrogen donor. Thus, N^{α}-(benzyloxycarbonyl)lysine in the presence of an equal weight of palladium black in 88% formic acid is completely deprotected in 30 s at room temperature.

Lower concentrations of formic acid in methanol also result in rapid removal of benzyl and benzyloxycarbonyl protecting groups but reduces the possibility of removal of acid labile protecting groups. Thus, as shown in Table I, 4.4% formic acid in methanol gives complete deprotection of both benzyl ester and benzyloxycarbonyl protecting groups in 5–10 min at room temperature. Under those conditions the *tert*-butyloxycarbonyl group appears to be quite stable as indicated by the 98% yield of (*tert*-butyloxycarbonyl)aspartic acid obtained from (*tert*-butyloxycarbonyl)aspartate β-benzyl ester (Table I). Thin layer chromatography of the product did not reveal the presence of any aspartic acid in the crude product.

The more refractory *N*-benzyl and nitro groups of N^{ϵ}-benzyllysine and nitroarginine are also removed under the same conditions but require approximately 10 and 5 h of reaction, respectively (Table I). Methionine-containing peptides give no particular difficulty. As shown in Table I, for example, the reaction with (benzyloxycarbonyl)-methionylglycine ethyl ester is complete in 10 min with a 92% yield. The reaction with *N*-(benzyloxycarbonyl)-*S*-benzylcysteinylphenylalanine ethyl ester, however, gave only a heterogenous mixture of products apparently due to incomplete reaction.

The results given in Table I demonstrate the feasibility of using formic acid as a hydrogen donor for the removal of *O*-benzyl, *N*-benzyl, and benzyloxycarbonyl protecting groups by catalytic transfer hydrogenation. The advantages of transfer hydrogenation over conventional hydrogenation have been described.[1-4] Formic acid, however, offers several additional advantages as compared to previously used hydrogen donors, and should be preferred in most cases. Thus, unlike cyclohexene or cyclohexadiene, formic acid is an excellent solvent for most peptides and peptide derivatives and therefore allows for complete solubilization of reactants and products in the great majority of cases. The reaction proceeds very rapidly at ambient temperature and pressure under relatively mild

(1) (a) G. M. Anantharamaiah and K. M. Sivanandaiah, *J. Chem. Soc., Perkin Trans. 1*, 5, 490 (1977); (b) G. M. Anantharamaiah, S. K. Balegidad and K. M. Sivanandaiah, Abstracts, 26th Congress of the International Union of Pure and Applied Chemistry, Tokyo, 1977, p 1123; (c) G. M. Anantharamaiah and K. M. Sivanandaiah, *Indian J. Chem., Sect. B*, 16, 797 (1978).

(2) A. E. Jackson and R. A. W. Johnstone, *Synthesis*, 685 (1976).

(3) (a) M. K. Anwer, S. A. Khan and K. M. Sivanandaiah, *Synthesis*, 75, (1978); (b) S. A. Khan and K. M. Sivanandaiah, *ibid.*, 750 (1978).

(4) A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki, and J. Meienhofer, *J. Org. Chem.*, **43**, 4194 (1978).

(5) A related paper describing the use of 98–100% formic acid and a palladium on charcoal catalyst to simultaneously remove benzyloxycarbonyl and *tert*-butyloxycarbonyl protecting groups came to our attention after the submission of this manuscript; K. M. Sivanandaiah and S. Gurusiddappa, *J. Chem. Res. (S)*, 108 (1979).

(6) G. Briefer and T. J. Nestrick, *Chem. Rev.*, 74, 567 (1974).

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