Synthesis of the Dihydrodiols and Diol Epoxides of Benzo[e]pyrene and Triphenylene

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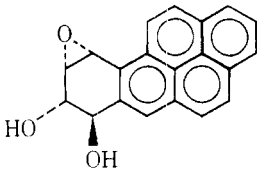
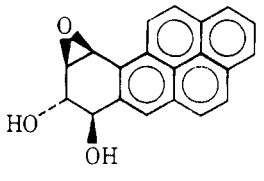
Synthesis of the "bay region" dihydrodiols of benzo[e]pyrene and triphenylene (1 and 2) and the corresponding anti isomeric diol epoxides (3 and 4) is described. NMR analysis indicates 1–4 exist preferentially in the diaxial conformation in contrast to the analogous derivatives of the potent carcinogen benzo[a]pyrene shown previously to exist preferentially as the diequatorial conformer. Both 3 and 4, derived from hydrocarbons inactive as carcinogens, are inactive as inhibitors of the ϕX 174 DNA virus, whereas the analogous *anti*-diol epoxide of benzo[a]pyrene is highly potent in this respect.

trans-7,8-Dihydroxy-*anti*-9,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (*anti*-BPDE) has been strongly implicated by several lines of evidence as the metabolically activated form of benzo[a]pyrene,[1] a potent carcinogen widespread in the environment.[2] Other recent studies point to analogous diol epoxide metabolites as the active forms of 3-methylcholanthrene,[6] benz[a]anthracene (BA),[7,8] 7-methylbenz[a]anthracene,[9] 7,12-dimethyl benz[a]anthracene,[10,11] chrysene,[12,13] 5-methylchrysene,[14] and dibenz[a,h]anthracene.[15] However, synthesis of these and other diol epoxides urgently required for biological studies has been achieved in only a few cases. Although the synthetic approaches initially devised for *syn*- and *anti*-BPDE[16] have subsequently been modified and improved[4,17,18] and extended to other polycyclic arenes,[4,13,17-19] the syntheses remain relatively complex, complicated by the special problems of isolation and purification of relatively reactive molecules.[4]

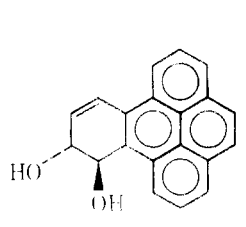


anti-BPDE



syn-BPDE

The present report describes the synthesis of the *trans*-dihydrodiols (1 and 2) and *anti*-diol epoxides (3 and 4) of benzo[e]pyrene (BeP) and triphenylene. While both 3 and 4 are close structural analogues of *anti*-BPDE, the parent hydrocarbons are considered to be inactive as carcinogens.[20] Consequently, these compounds are of interest for biological studies to determine differences, if any, in the patterns of metabolism of carcinogens and noncarcinogens. Specifically, it is of some importance to determine: (a) whether these dihydrodiols and diol epoxides can be formed by cells; (b) whether the latter are capable of alkylation of nucleic acids in vitro and in vivo; and (c) whether they are biologically active as mutagens, carcinogens, inhibitors of viral replication, etc.



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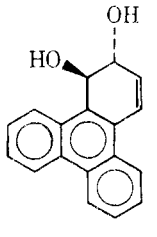

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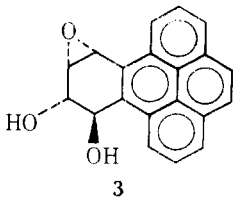

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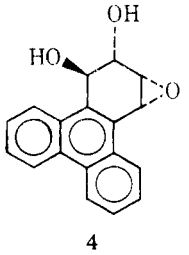

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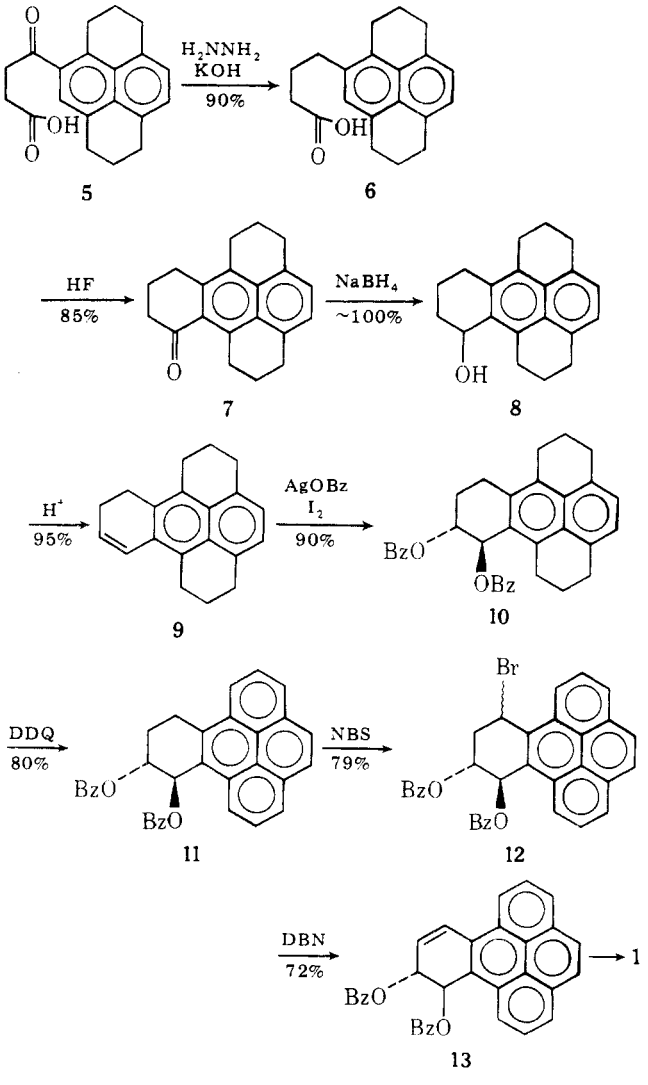
Results

Three synthetic routes to the *trans*-9,10-dihydrodiol of BeP (1) were explored. A key intermediate in all three was *trans*-

Scheme I. Synthesis of *trans*-9,10-dihydrobenzo[e]pyrene (1)



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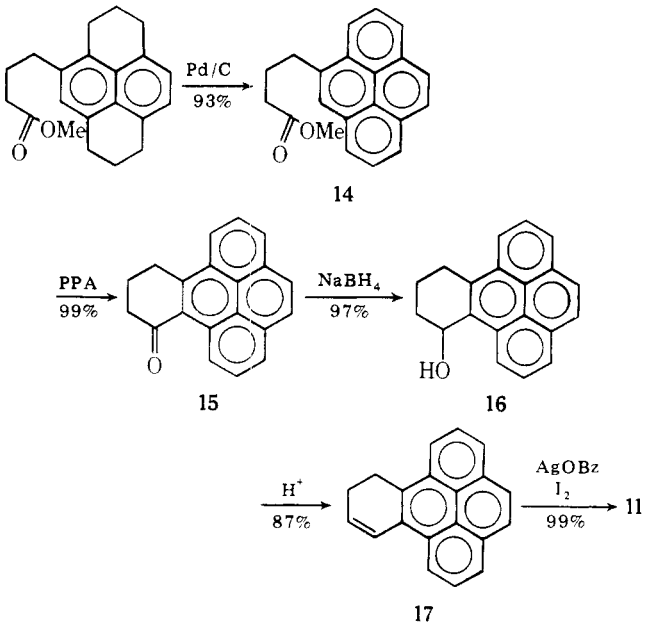
Scheme II. Alternative Synthesis of *trans*-9,10-Dihydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene Dibenzoate (11)



9,10-dibenzoyloxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene (**11**).

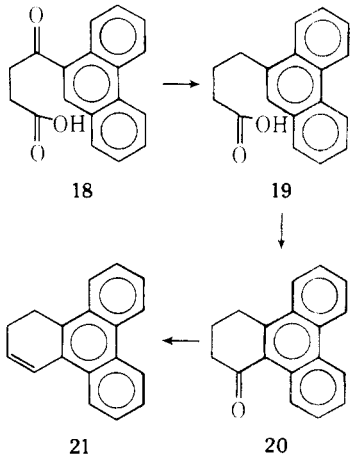
Synthesis of the latter was accomplished in optimum overall yield (58%) from β-(1,2,3,6,7,8-hexahydro-4-pyrenoyl)propionic acid (**5**) via the sequence depicted in Scheme I. Compound **5** was itself synthesized from pyrene through reduction with sodium and alcohol followed by condensation with succinic anhydride according to the method of Cook and Hewett.[21] Reduction of **5** by the Huang-Minlon modification of the Wolff-Kishner method gave the reduced acid **6**, cyclization of which in liquid HF provided the ketone **7**. Yields were 98 and 85%, respectively, marked improvements over those reported in the older literature[21] (52 and 29%, respectively) by other methods. Reduction of the carbonyl group of **7** with $NaBH_4$ furnished essentially quantitatively the corresponding alcohol **8**. Acid-catalyzed dehydration of the latter afforded cleanly 1,2,3,6,7,8,9,10-octahydrobenzo[*e*]pyrene (**9**), mp 129–130 °C; this structural assignment was supported by the integrated proton NMR spectrum, notably the H_{11} and H_{12} vinyl proton peaks at δ 6.20 and 6.80, respectively. Prévost reaction of **9** by the procedure utilized in our previous studies[4] gave the corresponding *trans*-diol dibenzoate **10**. The latter was converted smoothly to **11** on treatment with excess DDQ in refluxing benzene. The integrated proton NMR spectrum of **11** was in agreement with this structural assignment, which was further confirmed by microanalysis and by the identity of the melting point (219–220 °C) and other physical properties with those of the dibenzoate prepared by the alternative route outlined in Scheme II.

Conversion of **11** to the required dihydrodiol (**1**) and *anti*-diol epoxide of BeP (**3**) was accomplished by the general method previously utilized for the synthesis of analogous compounds.[4,13,16-19] Bromination of **11** with NBS in CCl_4 afforded a mixture of stereoisomeric bromodibenzoates (**12**) in high yield (99%). Since bromo compounds of this type are notoriously thermally unstable, no attempt was made to separate the isomers by fractional crystallization. Instead, the mixture was dehydrobrominated directly with DBN to *trans*-9,10-dibenzoyloxy-9,10-dihydrobenzo[*e*]pyrene (**13**). The 60-MHz NMR spectrum of **13** was consistent with this structural assignment exhibiting characteristic allylic (H_{10}) and vinylic (H_{11}) peaks at δ 5.98 and 6.75, respectively; the H_9 and H_{12} benzylic and vinylic proton signals were obscured somewhat by the aromatic protons, preventing their accurate assignment. The relatively small value of $J_{9,10}$ (2 Hz) is consistent with a trans-diequatorial relationship between these protons.[22] Treatment of **13** with sodium methoxide in methanol cleaved the benzoate ester groups to furnish the free dihydrodiol **1** as a white solid, mp 185–186 °C. The ^1H NMR spectrum of **1** exhibited benzylic, allylic, vinylic, and aromatic protons in the anticipated ratio, closely resembling the analogous region of the spectra of other *trans*-dihydrodiols.[4] The 100-MHz spectrum of the diacetate of **1** was nicely resolved with signals at δ 5.47 (H_{10}), 6.57 (H_{11}), 7.05 (H_9), and 7.81 (H_{12}) with appropriate couplings $J_{9,10}$ = 2.2, $J_{10,11}$ = 5.6, and $J_{11,12}$ = 10.5 Hz, consistent with this assignment. Finally, epoxidation of **1** with *m*-chloroperbenzoic acid afforded the *anti*-diol epoxide **3** as a white solid.

An alternative synthetic route to **11** involving aromatization prior to cyclization was also investigated (Scheme II). Dehydrogenation of the methyl ester of **6** over a 10% Pd/C catalyst at 220 °C afforded smoothly methyl γ-(4-pyrenyl)butyrate (**14**), mp 59–60 °C, in 93% yield. The NMR spectrum of **14** revealed aromatic, methylene, and methyl protons in the anticipated 9:6:3 ratio. Cyclization of **14** in polyphosphoric acid directly afforded the 9-keto derivative of 9,10,11,12-tetrahydrobenzo[*e*]pyrene (**15**), isolated virtually quantitatively from chromatography on Florisil as a yellow crystalline solid, mp 132–133 °C. Reduction of **15** with $NaBH_4$, followed by acid-catalyzed dehydration, provided 9,10-dihydrobenzo[*e*]pyrene (**17**), mp 123–124 °C (lit.[23] 124–126 °C). This structure was supported by the NMR spectrum, which exhibited a pair of vinylic peaks at δ 6.38 (d of t) and 7.40 (d) assigned to H_{11} and H_{12}, respectively; the observed couplings ($J_{10,11}$ = 4 Hz) were in accord with this assignment. Methylene, vinylic, and aromatic protons were also observed in the expected ratio (2:2:8). Finally, Prévost reaction of **17** furnished pure **11**, mp 215–216 °C, whose NMR spectrum was identical with that of the dibenzoate of *trans*-9,10-dihydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene synthesized by the method in Scheme I. The overall yield of **11** from **6** via the sequence in Scheme II was 68%.

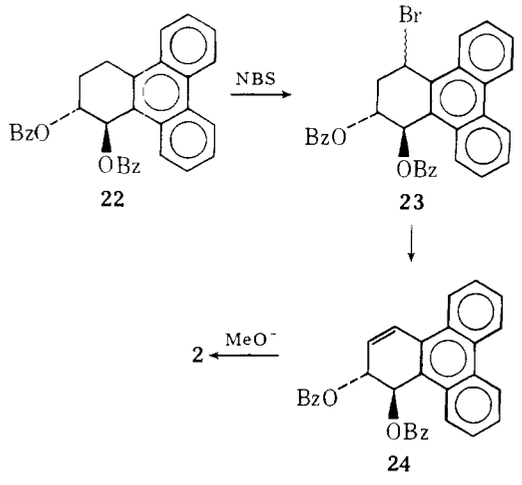
The third synthetic approach to **11** explored involved synthesis of 9,10-dihydrobenzo[*e*]pyrene from the parent hydrocarbon via catalytic hydrogenation to 9,10,11,12-tetrahydrobenzo[*e*]pyrene followed by dehydrogenation with DDQ. This method, described in a preliminary communication,[23] provides an efficient synthetic approach to a variety of dihydroarenes. In the present case, however, yields from both steps proved somewhat erratic and difficult to control and purification of products presented additional problems. Until these problems can be solved, this method is not recommended for synthesis of **11**.

Synthesis of 1,2-dihydrotriphenylene (**21**), the dihydroarene required as precursor of the *trans*-1,2-dihydrodiol of triphenylene (**2**), was accomplished via a sequence analogous to



that in Scheme II. The intermediate keto compound, 1-keto-1,2,3,4-tetrahydrotriphenylene (**20**), required for this purpose was synthesized from 9-bromophenanthrene through reaction of the corresponding Grignard reagent with succinic anhydride, followed by Clemmensen reduction and cyclization of the resulting acid **19** in liquid HF. The overall yield of **20** obtained via this sequence was superior to that reportedly obtained through a related sequence involving Wolff–Kishner reduction of the semicarbazone of **18** and cyclization of **19** with phosphoric oxide.[24] Reduction of **20** with $NaBH_4$ followed by acid-catalyzed dehydration of the resulting alcohol furnished 1,2-dihydrotriphenylene (**21**), mp 116 °C; this structural assignment was supported by microanalysis and by the integrated NMR spectrum, which exhibited aromatic, vinylic, benzylic, and allylic protons in the expected ratios. The H_4 vinylic proton appeared downfield in the aromatic region as a consequence of steric interaction with the aromatic peri hydrogen at the 5 position. This downfield shift is characteristic of bay region protons,[25] and was also seen for the hydrogen atoms in the 5, 8, 9, and 12 positions. The remaining vinylic proton, H_3, appeared as a well-resolved multiplet at δ 6.25 coupled to the H_4, CH_3, and H_1 protons ($J_{3,4}$ = 10 Hz; $J_{2,3}$ = 5 Hz).

Conversion of **21** to the dihydrodiol **2** was achieved through the general procedure employed for the synthesis of the analogous dihydrodiol of BeP (**1**). Prévost reaction of **21** furnished *trans*-1,2,3,4-tetrahydrotriphenylene (**22**). Bromination of the latter with *N*-bromosuccinimide followed by dehydrobromination with DBN[18] and methanolysis afforded **2**, mp 153–154 °C. Reaction of the latter with *m*-chloroperbenzoic acid by the standard procedure[4] gave *trans*-1,2-dihydroxy-*anti*-3,4-epoxy-1,2,3,4-tetrahydrotriphenylene (**4**). The structural and stereochemical assignments of **2**, **4**, and all intermediates, except the thermally unstable 4-bromo derivative **23**, are supported by microanalysis and by the NMR spectra of these compounds (cf. Discussion and Experimental Section). The spectra are also consistent with previously reported spectra of the analogous derivatives of other polycyclic hydrocarbons synthesized via analogous procedures.[4,13,16,17,19]



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Since the UV and fluorescence spectra are one of the principal means of identification of carcinogen metabolites, the spectra of **1** and **2** are presented in Figure 1. The UV spectra of the dihydrodiols matches closely those of the corresponding dihydroarenes.

Discussion

The foregoing syntheses of the *trans*-dihydrodiols (**1** and **2**) and *anti*-diol epoxides (**3** and **4**) of benzo[*e*]pyrene and triphenylene provide convenient synthetic approaches to these important hydrocarbon derivatives.

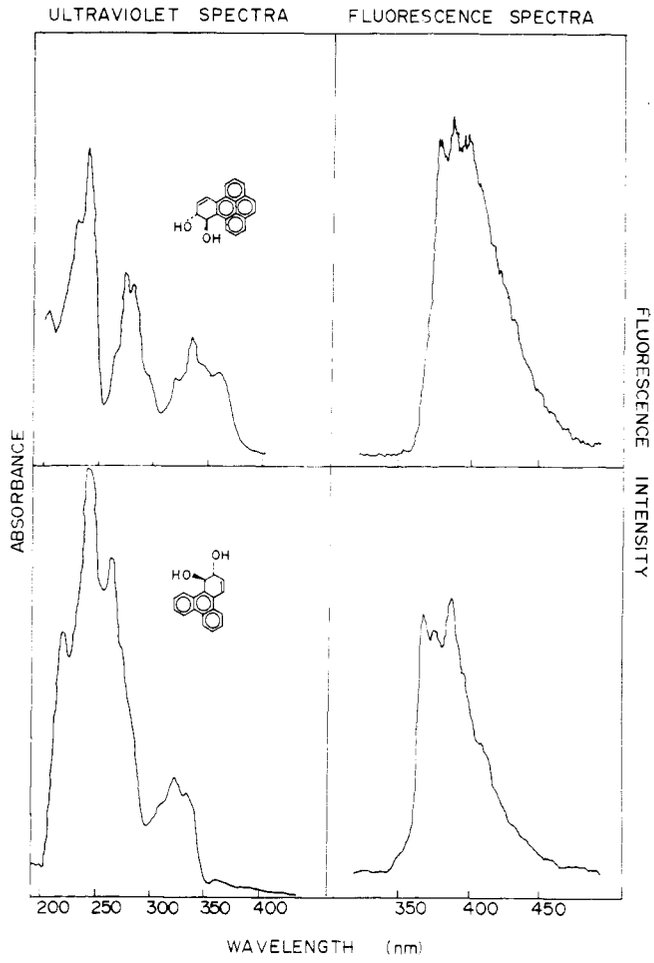
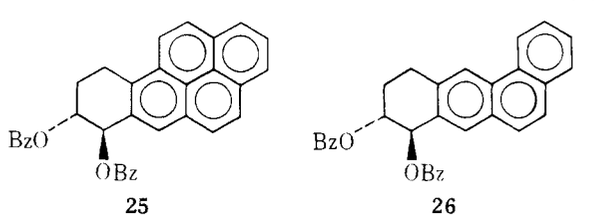


Figure 1. The ultraviolet and fluorescence spectra of **1** and **2** in ethanol were obtained on a Perkin-Elmer Model 512 spectrometer. Concentrations of **1** and **2** were 2.35×10^{-5} and 2.89×10^{-5} mol/L, respectively.

Attempted introduction of the olefinic bond into the tetrahydrodibenzoates **11** and **22** by means of DDQ failed, despite the fact that analogous reactions of the related tetrahydro dibenzoate esters **25** and **26** derived from benzo[*a*]pyrene and benz[*a*]anthracene proceed smoothly to provide high yields of the corresponding dihydrodibenzoates.[4,17a] This difference in reactivity probably results from the fact that in both **11** and **22** the bulky diester groups are in bay regions and are forced by steric interaction with the adjacent aromatic ring into the trans-diaxial conformation B. In contrast, in both **25** and **26** the diester groups are free to adopt the diequatorial conformation A. Consequently, hydride abstraction by DDQ[26]



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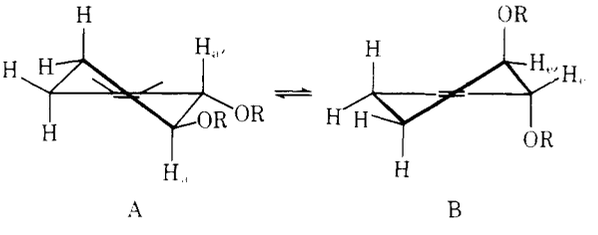


Table I. Proton NMR Data[a] on the Dihydrodiols (1 and 2) and *anti*-Diol Epoxides (3 and 4) of Benzo[e]pyrene and Triphenylene

compd	registry no.	δ benzylic carbinol	δ other carbinol	J, Hz
1	66788-06-5	5.52	4.52	$J_{9,10}$ = 1.8
2	68151-04-2	5.23	4.63	$J_{1,2}$ = 1.0
3	68151-05-3	5.72	4.88	$J_{9,10}$ = 3.0
4	68151-06-4	5.30	4.50	$J_{1,2}$ = 1 5

[a] Spectra taken on Varian T-60 and/or Bruker 270 MHz spectrometers in acetone-d_6; chemical shifts are in parts per million relative to Me_4Si. To aid spectral interpretation, diols were converted to their dideuterio derivatives by addition of D_2O. Further details of the NMR spectra are reported in the Experimental Section.

from the benzylic axial positions of **11** and **22** is effectively blocked by steric interaction between the bulky reagent and the axially oriented ester groups, while steric approach to **25** and **26** lacks such hindrance.

The NMR spectra of the diesters support this interpretation. Thus, the observed couplings between the carbinol diester protons of **11** and **22** are $J_{9,10}$ = 3.5 and $J_{1,2}$ = 2.5 Hz, respectively. Drieding stereomodels of these compounds give a dihedral angle of ~70° for protons $H_{e,e'}$ of the diaxial conformer B and ~170° for protons $H_{a,a'}$ of the diequatorial structure A. Calculated coupling constants based on these values and the Karplus relationship as modified by Bothner-By[27] are J = 2.82 and 12.21 Hz, respectively. The close agreement between the former calculated value and the observed couplings for **11** and **22** is consistent with existence of **11** and **22** essentially exclusively in the diaxial conformation B. In contrast, the observed analogous couplings for **25** and **26** are $J_{7,8}$ = 5.5 Hz[28] and $J_{8,9}$ = 6.0 Hz,[29] respectively, indicating existence of these molecules as equilibrium mixtures predominantly in the diequatorial conformation A.

The dihydrodiols (**1** and **2**) and diol epoxides (**3** and **4**) of benzo[e]pyrene and triphenylene, like the tetrahydrodibenzoates **11** and **22**, appear on the basis of the NMR data to exist in preferred diaxial conformations. Thus, the observed couplings between the carbinol protons of these compounds all lie in the range of J = 1–3 Hz (Table I). Previous studies indicate that the analogous dihydrodiols and diol epoxides of benzo[a]pyrene and benz[a]anthracene, in which the dihydrodiol function is not sterically constrained in a bay region, exist preferentially in the alternative diequatorial conformation.[16,17a,28,29] The significance of this conformational difference with respect to the biological activity is not at present known. However, it is conceivable that the diaxial orientation of the hydroxyl groups in **3** and **4** and in other diol epoxides having the dihydrodiol function in a bay region may alter the rate or the site of covalent binding with DNA and RNA.

Biological Activity

Preliminary experiments indicate that the two *anti*-diol epoxides **3** and **4** are inactive, or only weakly active, as inhibitors of the infectivity of the φX 174 DNA virus in *E. coli* spheroplasts.[30] Since inhibition of viral activity is believed to result from direct covalent interaction of the inhibitor with viral DNA,[30] it would appear that the diol epoxide structures **3** and **4** react relatively inefficiently, if at all, with viral nucleic acids. This finding is in accord with the "bay region theory" of Jerina et al.,[31] which predicts on the basis of the difference in delocalization energies (ΔE_{deloc}) between the ionized and un-ionized forms of arene diol epoxides that diol epoxides having the epoxide ring in a bay region should exhibit exceptional reactivity. They further propose that this structural feature is characteristic of the active diol epoxide metabolites of carcinogenic hydrocarbons. However, a number of exceptions to this hypothesis have already been noted,[32] and recent evidence suggests that carcinogenic hydrocarbons give rise to multiple active metabolites in addition to the bay region diol epoxides.[34]

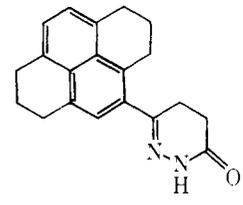
Biological studies of carcinogenic and mutagenic activity and in vitro covalent binding to nucleic acids are in progress and will be reported separately.

Experimental Section

General. Triphenylene and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) were purchased from the Aldrich Chemical Co. BeP was purchased from the Research Organic/Inorganic Chemical Corp. β-(1,2,3,6,7,8-Hexahydro-4-pyrenoyl)propionic acid (**5**)[21] and β-(9-phenanthroyl)propionic acid (**18**)[24] were synthesized by published procedures. *N*-Bromosuccinimide (NBS) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were supplied by Arapahoe Chemical Co.; NBS was crystallized from water prior to use. *m*-Chloroperbenzoic acid was obtained from the Aldrich Chemical Co., and purified by washing with phosphate buffer of pH 7.5 and drying under reduced pressure. The NMR spectra were obtained on Varian T 60 or Bruker HX 270 spectrometers with tetramethylsilane as internal standard in $CDCl_3$ unless specified otherwise. Melting points are uncorrected. All new compounds gave satisfactory microanalyses for C, H within ±0.3% and/or mass spectra consistent with the assigned structures.

γ-(1,2,3,6,7,8-Hexahydro-4-pyrenyl)butyric Acid (6). A solution of the keto acid **5** (1.45 g, 4.73 mmol), KOH (1.04 g), and anhydrous hydrazine (1.45 g) in diethylene glycol (25 mL) dried over molecular sieves was heated at reflux for 4 h. The reaction mixture was diluted with water and acidified with concentrated hydrochloric acid, and the resulting white precipitate was collected and washed with water, giving 1.26 g (90%) of the reduced acid **6**, mp 176–178 °C (lit.[21] 178 °C).

Repetition of the foregoing reaction with 17.85 g of **5** using hydrazine hydrate (J. T. Baker, 99–100%) under the same conditions afforded 16.8 g of the phthalazinone intermediate (**27**) as a white solid. Recrystallization from benzene gave pure **27**: mp 214–216 °C; NMR δ 2.07 (m, 4, $H_{2,7}$), 2.97 (m, 12), 7.18 (m, 3, aromatic), and 8.8 (s, 1); mass spectrum (70 eV) *m/e* 304.



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Decomposition of **27** (5.47 g, 18 mmol) with KOH (6 g) in refluxing diethylene glycol (150 mL) for 6 h gave upon acidification 5.29 g (99%) of **6**, mp 175–178 °C (lit.[21] 178 °C).

9-Oxo-1,2,3,6,7,8,9,10,11,12-decahydrobenzo[e]pyrene (7). Anhydrous HF (20 mL) was condensed in a polystyrene bottle containing **6** (1 g) and the resulting solution was stirred magnetically for 18 h. Then HF was removed in a stream of N_2 and the residue was taken up in 1:1 ethyl acetate–ether (200 mL), washed with 5% aqueous sodium carbonate solution (2 × 100 mL), and water and dried. Removal of the solvent gave the crude ketone (900 mg), which was dissolved in benzene and chromatographed on silica gel. Elution with benzene followed by crystallization from ethanol gave pure **7** (800 mg): mp 147–148 °C (lit.[21] 147–148 °C); NMR δ 1.8–2.0 (m, 6, aliphatic), 2.5–3 (m, 10, benzylic), 3.4–3.6 (m, 2, CH_2CO), and 7.0 (br s, 2, aromatic); IR ($CHCl_3$) 1672 cm^{-1} (C=O).

9-Hydroxy-1,2,3,6,7,8,9,10,11,12-decahydrobenzo[e]pyrene (8). To a solution of the above ketone (1 g) in methanol (100 mL) was added $NaBH_4$ (1 g) in small portions with stirring. After 1 h, the solvent was evaporated under reduced pressure. Crude **8** (1 g) was isolated by a conventional workup procedure and used directly in the next step.

1,2,3,6,7,8,9,10-Octahydrobenzo[e]pyrene (9). A solution of **8** (400 mg) in glacial acetic acid (15 mL) with 1 drop of concentrated hydrochloric acid was heated at 90 °C under N_2 for 1 h. The solution was cooled and diluted with water (50 mL). The precipitated solid was filtered, washed with water, and dried. The crude olefin (370 mg) thus

obtained was dissolved in benzene and chromatographed on Florisil. Elution with hexane gave essentially pure **9**, which was recrystallized from benzene–ethanol to provide the analytical sample of **9**: mp 129–130 °C; NMR δ 1.8–2.6 (m, 6), 2.6–3.3 (m, 10, benzylic), 6.20 (m, 1, H_{11}), 6.80 (m, 1, H_{12}), and 7.1 (s, 2, $H_{4,5}$); $J_{11,12} = 10$, $J_{10,11} = 4$, $J_{10,12} \simeq 1$ Hz.

***trans*-9,10-Dibenzoyloxy-1,2,3,6,7,8,9,10,11,12-decahydrobenzo[*e*]pyrene (10).** A mixture of silver benzoate (1.43 g, 4.3 mmol) and I_2 (560 mg, 2.20 mmol) in dry benzene (50 mL) was stirred under reflux until the red color disappeared. A solution of **9** (376 mg, 1.45 mmol) in dry benzene (20 mL) was added, and the resulting suspension was stirred at reflux for 16 h. The product was filtered hot and washed with hot ethyl acetate. The combined filtrate was extracted with cold 10% aqueous NaOH (2 × 30 mL), washed with water, and dried, and the solvent was evaporated. The residue was dissolved in benzene and chromatographed on silica gel. Elution with hexane gave unreacted **9** (30 mg). Further elution with benzene afforded the dibenzoate (650 mg, 90%), recrystallization of which from acetone–ethanol furnished pure **10**: mp 125–126 °C; NMR δ 2.0–2.70 (m, 6, aliphatic), 3.0–3.20 (m, 10, benzylic), 5.80 (m, 1, H_{10}), 6.70 (d, 1, $J_{9,10} = 2.5$ Hz, H_9), 7.4–7.6 (m, 7, aromatic), and 8.0–8.2 (m, 5, aromatic).

***trans*-9,10-Dibenzoyloxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene (11).** To a solution of **10** (240 mg, 0.5 mmol) in dry benzene (50 mL) under N_2 was added DDQ (390 mg, 1.7 mmol) with stirring, and the resulting solution was heated at reflux for 1 h. The reaction mixture was cooled, filtered through Celite, and washed with benzene, and the combined extracts were washed with 5% aqueous sodium metabisulfite solution (2 × 100 mL), water, 5% aqueous NaOH (2 × 100 mL), and water, dried and evaporated to dryness. The crude product was taken up in benzene and chromatographed on silica gel. Elution with benzene gave **11** (200 mg); recrystallization from acetone–ethanol gave pure **11**: mp 219–220 °C; NMR (270 MHz) δ 2.67 (m, 2, H_{11}), 3.50 (heptet, 1, $H_{12'}$), 3.70 (q, 1, H_{12}), 6.21 (q, 1, H_{10}), 7.16 (d, 1, H_9), and 7.22–8.48 (m, 18, aromatic); $J_{9,10} = J_{10,11} \simeq 3.5$, $J_{11,12} = 6$, $J_{11',12} \simeq 1$, $J_{12,12'} = 17$, $J_{12',11} = 11$, $J_{11',12'} = 6$ Hz.

***trans*-9,10-Dibenzoyloxy-9,10-dihydrobenzo[*e*]pyrene (13).** A suspension of NBS (392 mg, 2.2 mmol) in a solution of **11** (1 g, 2 mmol) and benzoyl peroxide (10 mg) in CCl_4 (200 mL) was heated at reflux under a heat lamp for 1.5 h under N_2. Conventional workup provided **12** (1.14 g, 99%) as a yellow solid: NMR δ 3.20 (m, 2, H_{11}), 5.8–6.38 (m, 2, $H_{10,12}$), and 7.1–8.8 (m, 19, H_9 and aromatic).

To a solution of **12** (1.14 g, 2 mmol) in THF (100 mL) at 0 °C was added DBN (10 mL). The resulting solution was stirred at 4 °C for 3 h, ethyl acetate (300 mL) and ether (200 mL) were added, and the solution was extracted successively with water, 2% aqueous acetic acid, water, dilute $NaHCO_3$ solution, and water, dried, and concentrated to give **13** (722 mg, 72%) as an off-white solid: mp 175–177 °C; NMR δ 5.98 (d of d, 1, H_{10}), 6.75 (q, 1, H_{11}), and 7.1–8.7 (m, 20, $H_{9,12}$ and aromatic); $J_{9,10} = 2$, $J_{10,11} = 5.5$, $J_{11,12} = 10$ Hz.

***trans*-9,10-Dihydroxy-9,10-dihydrobenzo[*e*]pyrene (1).** Sodium methoxide (5.24 mmol) was added to a solution of dibenzoate **13** (650 mg, 1.31 mmol) in THF (40 mL) and methanol (20 mL) under N_2, and the solution was stirred for 30 min at 65 °C. Ether was added and the resulting solution was washed with water, dried, and concentrated under vacuum. Recrystallization of the crude product from $CHCl_3$ gave pure **1** (200 mg, 54%) as an off-white solid: mp 185–186 °C; NMR (acetone-d_6) δ 4.52 (d of d, 1, H_{10}), 5.52 (apparent s, 1, H_9), 6.52 (q, 1, H_{11}), 7.67 (d, 1, H_{12}), and 7.97–8.60 (m, 8, aromatic); $J_{9,10} = 1.8$, $J_{10,11} = 5$, $J_{11,12} = 10$ Hz.

***trans*-9,10-Dihydroxy-*anti*-11,12-epoxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene (3).** A solution of **1** (40 mg, 0.14 mmol) and *m*-chloroperbenzoic acid (400 mg) in 20 mL of dry THF was stirred under N_2 at room temperature for 1.5 h. The product was diluted with ether, washed with 10% aqueous NaOH (2×) and water, and dried ($MgSO_4$). Evaporation of the solvent avoiding heating, followed by trituration with ether, gave **3** (33 mg, 79%) as a white solid: NMR (acetone-d_6) δ 4.25 (m, 1, H_{11}), 4.88 (m, 1, H_{10}), 5.31 (d, 1, H_{12}), 5.72 (apparent s, 1, H_9); $J_{9,10} = 3$, $J_{10,11} = 4.5$, $J_{11,12} = 4.5$ Hz.

Methyl γ-(1,2,3,6,7,8-Hexahydro-4-pyrenyl)butyrate (Methyl-6). A solution of **6** (9.8 g, 18 mmol) and concentrated HCl (1 mL) in methanol (800 mL) was stirred overnight at room temperature. Conventional workup provided crude methyl-**6**, which was purified by chromatography on a column of Florisil. Elution with 1:1 benzene–ether furnished methyl-**6** (8.75 g, 88%) as a white solid: mp 58–59 °C; NMR δ 1.8–3.2 (m, 18), 3.65 (s, 3, CH_3), 7.02 (s, 2, $H_{9,10}$), and 6.98 (s, 1, H_5).

Methyl 4-Pyrenylbutyrate (14). Methyl-**6** (8.75 g, 28 mmol) and 875 mg of 10% Pd/C were heated at 220 °C for 3 h under N_2. The product was taken up in acetone, filtered to remove the catalyst, reconcentrated, and chromatographed on a column of Florisil. Elution with ether–benzene (1:1) afforded **14** as a white solid (8.03 g, 93%) melting at 59–60 °C after recrystallization from ethyl acetate–hexane (1:4): NMR δ 1.93–2.54 (m, 4), 3.15 (t, 2), 3.56 (s, 3, CH_3), and 7.87 (m, 9, aromatic).

9-Oxo-9,10,11,12-tetrahydrobenzo[*e*]pyrene (15). The ester **14** (8.0 g, 26.5 mmol) was dissolved in polyphosphoric acid (300 mL) and heated under N_2 for 3 h at 110 °C. The reaction mixture was poured into ice–water and extracted with ethyl acetate. Conventional workup followed by chromatography on Florisil eluted with 1:1 benzene–ether afforded a yellow solid (7.12 g, 99%) identified as **15**: mp 132–133 °C; NMR δ 2.21 (quintet, 2, H_{11}), 2.78 (t, 2, H_{10}), 3.24 (t, 2, H_{12}), 7.52–8.19 (m, 7, aromatic), and 9.63 (dd, 1, H_8).

9-Hydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene (16). A solution of the ketone **15** (8.20 g, 22.5 mmol) in THF (100 mg) and methanol (400 mL) was stirred with $NaBH_4$ (4.3 g) at ambient temperature for 2.5 h. After evaporation of the solvent, water was added, and the resulting yellow solid was washed with water and dried in vacuo to afford **16** (7.95 g, 97%): NMR δ 1.8–2.5 (m, 4, $H_{10,11}$), 2.98–3.40 (m, 2, H_{12}), 5.6 (m, 1, H_9), 7.8–8.68 (m, 8, aromatic and OH). This was employed directly in synthesis of **17**.

9,10-Dihydrobenzo[*e*]pyrene (17). A solution of **16** (7.95 g, 29 mmol) and *p*-toluenesulfonic acid (600 mg) in benzene (250 mL) was heated at reflux for 1 h. Conventional workup followed by chromatography on silica gel eluted with hexane–benzene (4:1) afforded **17** as a yellow solid (6.04 g, 87%): mp 123–124 °C (lit.[23] 124–126 °C); NMR δ 2.63 (m, 2, H_{10}), 3.37 (apparent t, 2, H_9), 6.38 (d of t, 1, H_{11}), 7.40 (d, 1, H_{12}), and 7.9–8.87 (m, 8, aromatic); $J_{9,10} = 9$, $J_{10,11} = 4$, $J_{11,12} = 10$ Hz.

Prévost Reaction of 17. A suspension of silver benzoate (2.93 g, 12.72 mmol) in a solution of I_2 (1.616 g, 6.36 mmol) in benzene (200 mL) was heated at reflux under N_2. To this was added **17** (1.335 g, 5.3 mmol) and reaction was maintained at reflux for 24 h. The precipitate of silver iodide was filtered off from the hot solution and washed with hot benzene, and the filtrate was concentrated under vacuum. The product was crystallized from ethyl acetate–hexane giving 2.6 g (99%) of the dibenzoate **11**: mp 219–220 °C; the NMR spectrum was identical with that obtained via the alternative route.

γ-(9-Phenanthryl)butyric Acid (19). Clemmensen reduction of the keto acid **18**[24] (2 g) by a standard procedure[35] provided the reduced acid **19** (1.4 g), mp 173–174 °C, recrystallized from ethanol (lit.[24] 173–174 °C) in 70% yield.

1-Oxo-1,2,3,4-tetrahydrotriphenylene (20). Cyclization of **19** (1 g) in anhydrous HF (20 mL) following the usual procedure afforded the ketone **20** (0.82 g, 80%), mp 98–99 °C, recrystallized from methanol (lit.[24] 101 °C): NMR δ 1.93 (quintet, 2, H_3), 2.60 (t, 2, H_2), 2.90 (t, 2, H_4), 5.5–8.0 (m, 5, aromatic), 8.33 (m, 2, $H_{8,9}$), and 9.28 (m, 1, H_{12}); assignment of H_2 and H_3 may possibly be reversed.

1,2-Dihydrotriphenylene (21). To a solution of the ketone **20** (1.45 g) in methanol (100 mL) was added $NaBH_4$ (1.45 g) in small portions with stirring. After 1 h the solvent was removed under reduced pressure and the product was worked up by a conventional procedure. The crude product was recrystallized from ethyl acetate–hexane to provide 1-hydroxyl-1,2,3,4-tetrahydrotriphenylene (1.49 g, 90%): mp 120 °C; NMR δ 2.10 (m, 5, $H_{1,2,3}$), 3.20 (m, 2, H_4), 5.40 (s, 1, OH), 7.75 (m, 4, $H_{6,7,10,11}$), 8.50 (m, 2, $H_{5,12}$), and 8.90 (m, 2, $H_{8,9}$).

A solution of the alcohol (1.4 g) in acetic acid (30 mL) with 1 drop of concentrated HCl was heated at 90 °C under N_2 for 1 h. The solution was cooled and diluted with cold water (100 mL). The solid precipitated was removed by filtration, washed with water, dried, taken up in benzene, and chromatographed on Florisil. Elution with hexane gave pure **21** (1.1 g, 70%): mp 116 °C; NMR δ 2.35 (m, 2, H_2), 3.05 (m, 2, H_1), 6.25 (m, 1, H_3), 7.55 (m, 5, $H_{4,6,7,10,11}$), 8.05 (m, 2, $H_{5,12}$), and 8.75 (m, 2, $H_{8,9}$); $J_{2,3} = 5$, $J_{3,4} = 10$ Hz.

***trans*-1,2-Dibenzoyloxy-1,2,3,4-tetrahydrotriphenylene (22).** A mixture of silver benzoate (1.5 g, 7 mmol) and I_2 (0.65 g, 3.5 mmol) in dry benzene (50 mL) was stirred under reflux until the red color disappeared. A solution of **21** (0.74 g, 3.3 mmol) in 25 mL of dry benzene was added and the resulting suspension was stirred under reflux for 16 h. The product was filtered hot through Celite and washed with 3 × 25 mL of hot ethyl acetate. The combined filtrates were extracted with cold 10% aqueous NaOH (2 × 50 mL), washed with H_2O (3 × 100 mL), and dried, and solvent was removed. The residue was dissolved in benzene and chromatographed on silica gel. Elution with hexane gave unreacted hydrocarbon (0.26 g). Further elution with benzene gave **22**, recrystallization of which from acetone–ethanol provided pure **22** (0.93 g, 65%): mp 206 °C; NMR δ 2.76 (m, 2, H_3), 3.75 (m, 2, H_4), 6.05 (dd, 1, H_2), 7.25 (d, 1, H_1), 7.40–8.50 (m, 16, aromatic), and 8.90 (m, 2, $H_{8,9}$); $J_{1,2} = 2.5$ Hz.

***trans*-1,2-Dibenzoyloxy-1,2-dihydrotriphenylene (24).** NBS (0.18 g, 1 mmol), **22** (472 mg, 1 mmol), and azoisobutyronitrile (2 mg)

were heated in refluxing CCl_4 (20 mL) for 40 min. Conventional workup afforded the crude monobromo derivative (attempted purification resulted in extensive decomposition). The residue was treated with DBN (0.2 mL) using a procedure similar to that employed for 1-dibenzoate. Workup using ether in place of ethyl acetate furnished **24** (0.23 g, 50%); recrystallization from acetone gave pure **24**: mp 172–173 °C; NMR δ 5.86 (d, 1, H_2), 7.23–8.32 (m, 18, aromatic and $H_{1,4}$), and 8.71 (m, 2, $H_{8,9}$); $J_{1,2} = 2$, $J_{2,3} = 6$, $J_{3,4} = 11$ Hz.

***trans*-1,2-Dihydroxy-1,2-dihydrotriphenylene (2).** To a solution of **24** (230 mg, 0.5 mmol) in anhydrous THF (15 mL) was added a solution of $NaOCH_3$ (0.11 g, 2 mmol) in methanol (3 mL). The solution was heated at 65 °C for 30 min, cooled, and partitioned between water and ether. The combined ether extracts were dried and evaporated to dryness. The residue was triturated with 5 mL of ether–hexane (1:1) to afford **2** (0.11 g, 90%): mp 153–154 °C; NMR (270 MHz) δ 4.63 (t, 1, H_2), 5.05 (d, 1, OH_2), 5.23 (d, 1, H_1), 5.28 (d, 1, OH_1), 6.41 (dd, 1, H_3), 7.55 (d, 1, H_4), 7.76 (m, 4, $H_{6,7,10,11}$), 8.34 (m, 1, $H_{5 \text{ or } 12}$), 8.42 (m, 1, $H_{5 \text{ or } 12}$), and 8.91 (m, 2, $H_{8,9}$); $J_{1,2} = 1$, $J_{2,3} = 6$, $J_{3,4} = 9$ Hz.

***trans*-1,2-Dihydroxy-*anti*-3,4-epoxy-1,2,3,4-tetrahydrotriphenylene (4).** Epoxidation of **2** (130 mg) was conducted following essentially the same procedure for synthesis of **3**. The crude product was triturated with ether to provide **4** (92 mg, 60%): NMR (270 MHz) δ 4.50 (dd, 1, H_2), 4.51 (d, 1, OH_2), 4.68 (t, 1, H_3), 5.04 (d, 1, OH_1), 5.20 (d, 1, H_4), 5.30 (t, 1, H_1), 7.72 (m, 4, $H_{6,7,10,11}$), 8.40 (m, 1, $H_{5 \text{ or } 12}$), 8.52 (m, 1, $H_{5 \text{ or } 12}$), and 8.85 (m, 2, $H_{8,9}$); $J_{1,2} = 1.5$, $J_{2,3} = 4.5$, $J_{3,4} = 4$, $J_{1,OH} = J_{2,OH} = 4.5$ Hz.

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Note Added in Proof. Studies of nucleic acid binding indicate that the benzo[e]pyrene *anti*-diol epoxide **3** binds relatively efficiently to DNA (N. Geacintov et al., manuscript in preparation), contrary to prediction of the bay region theory. Fluorescence quenching experiments indicate that the polycyclic aromatic ring system of the product of binding of **3** to DNA is intercalated between the nucleic acid–base pairs. This contrasts with the results of similar experiments with *anti*-BPDE which show that the bound hydrocarbon resides in the minor groove of the DNA helix. [T. Prusik, N. Geacintov, C. Tobiasz, V. Ivanovic, and I. B. Weinstein, *Photochem. Photobiol*, in press.] This difference may be significant in relation to the wide difference in carcinogenic activity between the parent hydrocarbons.

Registry No.—**5**, 68151-07-5; **6** 66787-94-8; methyl-**6**, 66787-95-9; **7**, 68151-08-6; **8**, 68151-09-7; **9**, 68151-10-0; **10**, 68151-11-1; **11**, 68151-12-2; **12**, 68151-13-3; **13**, 68151-14-4; **14**, 66787-96-0; **15**, 66787-97-1; **16**, 66788-00-9; **17**, 66788-01-0; **18**, 68151-15-5; **19**, 68151-16-6; **20**, 68151-17-7; **21**, 68151-18-8; **22**, 68151-19-9; **23**, 68151-23-5; **24**, 68151-20-2; **27**, 68151-21-3; 1-hydroxy-1,2,3,4-tetrahydrotriphenylene, 68151-22-4; silver benzoate, 532-31-0.

References and Notes

(1) Following the initial publication by Sims et al. of evidence that a 7,8-dihydrodiol 9,10-epoxide is the major metabolic intermediate of benzo[a]pyrene which binds covalently to DNA in vivo,[3] there has been explosive growth of the literature in this field. Major significant contributions have been made by the research groups of Brookes, Conney, Gelboin, Harvey, Jerina, Sims, and Weinstein. For leading references the interested reader is referred to the recent reviews[4,5] on this topic and to the recent publications cited in the following references.
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