(2); C1 0.009 (8); C2, −0.013 (9); C3, 0.007 (10) Å); W2 is out of this plane by −0.108 Å. W1 is above this plane and the three W1–C*i* bond lengths are not significantly different from each other with a mean value of 2.342 (5) Å. The W1–P bond length of 2.550 (2) Å is somewhat longer than 2.512 (2) Å, the W2–P bond length which is in the range of those found elsewhere. The C7–C12 phenyl ring lies on the opposite side of the PC_3 plane with respect to the $W1(CO)_4$ group and its mean plane makes a dihedral angle of 106.6 (2)° with the PC_3 mean plane. The PC_3 system seems to be fully delocalized: the two C$\overset{..}{-}$C bond lengths are nearly equal (respectively 1.442 (11) and 1.414 (11) Å for the central and terminal bonds) and the P–C bond is short (1.783 (8) Å vs. 1.84 Å for a single P–C bond length, compare with the structure of a η^5-phosphacyclopentadienyl-$W(CO)_3I$ complex[15]).

We are currently starting to develop the chemistry of these new η^4-phosphabutadiene complexes.

Supplementary Material Available: Table I, positional parameters and their estimated standard deviations for all non-hydrogen atoms; Table II, U_{ij} with their estimated standard deviations; Table III, positional parameters for the hydrogen atoms; Table IV, bond distances with their estimated standard deviations; and Table V, bond angles with their estimated standard deviations (8 pages); Table VI, observed and calculated structure factor amplitudes (×10) for all observed reflections (17 pages). Ordering information is given on any current masthead page.

Dramatic Solvent and Stereoelectronic Effects in a Biomimetic Oxidation: 9,10-Dialkylanthracenes

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7,12-Dimethylbenz[*a*]anthracene (DMBA) and other alkylated aromatics undergo ring oxygenation in the presence of rat-liver microsomes containing the ubiquitous cytochrome P_{450} to yield a dihydroepoxy diol.[1] The water-soluble fraction from the same tissue, i.e., cytosol, yields not ring oxygenation but methyl hydroxylation (see Figure 1).[2] This diversity has been interpreted in terms of a dichotomy between direct ring oxygenation in the former case and one-electron oxidation to a radical cation in the latter. Because of their high acidity, such radical cations undergo rapid deprotonation leading ultimately to formation of hydroxymethyl products.[3] Thus the absence of such products during oxidation of DMBA by cytochrome P_{450} is difficult to reconcile with the known propensity of this enzyme to form radical cations of higher potential hydrocarbons.[4] We now report results on the oxidation of the title compounds which suggest that this dichotomy is the result of a solvent effect.

Our curiosity was stimulated by the divergent biochemistry of the structurally analogous yet noncarcinogenic 7,12-diethylbenz[*a*]anthracene and 6-ethylbenzo[*a*]pyrene.[5] These possible "changes in metabolism"[5] might have their origin in a stereoelectronic effect inhibiting facile deprotonation of the ethyl group of the radical cation, which is maintained perpendicular to the aromatic plane by the presence of significant peri interactions.[6] Thus use of a substrate, 9-ethyl-10-methylanthracene, which incorporated both features, should allow us to quantitatively assess the importance of such a stereoelectronic effect by determining the relative ratio of hydroxymethyl- to 1-hydroxyethyl-substituted anthracenes upon one-electron oxidation.

Treatment of a 3 mM solution of 9,10-dimethylanthracene (DMA), 9-ethyl-10-methylanthracene (EMA), and 9,10-diethylanthracene (DEA) with tris(phenanthroline)tris(hexafluorophosphate)iron in 10:90 water acetonitrile[7] under argon

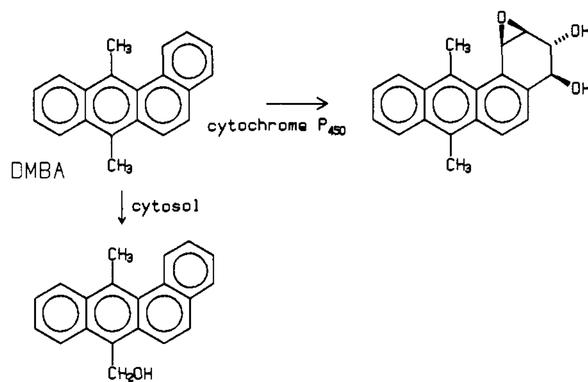

Figure 1. Ring vs. side-chain oxidation in DMBA oxidation.

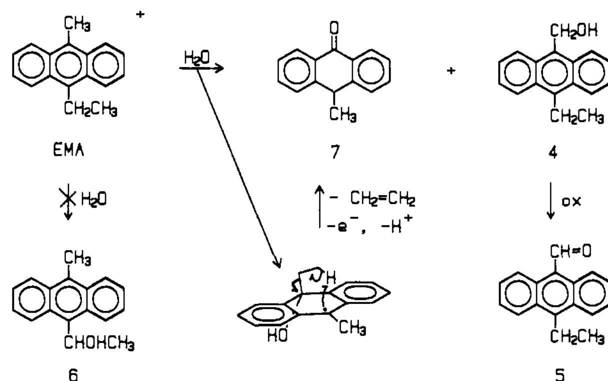

Figure 2. Oxidation of EMA.

Table I. Effect of $[H_2O]$ on Oxidation of 9-Ethyl-10-methylanthracene[a]

$[H_2O]$, M	% yield[b] 4	5	7
2.78	11.1	4.0	76.5
5.56	24.9	5.7	62.9
8.33	37.1	7.0	50.2
11.1	46.2	8.4	40.6
rat-liver microsomes[c,d]			
1 h	3.2		83.4
20 h	4.1		77.3
rat-liver cytosol[c]			
20 h	85.7		8.9

[a] Reaction in 20 mL of H_2O-MeCN with 3.00 mM 9-ethyl-10-methylanthracene (EMA) and 4.5 mM tris(phenanthroline)tris(hexafluorophosphate)iron at 25 °C for 30 min was followed by ether precipitation of iron salts. [b] Yields based upon recovered starting material. [c] Solutions of dialkylanthracene in 20% aqueous dimethylformamide were incubated at room temperature (ca. 25 °C). [d] Anthraquinone was also formed in yields of 6.5% (1 h) and 10.7% (20 h). No oxidation was observed with denatured enzyme.

(1) (a) Lee, H.; Harvey, R. G. *J. Org. Chem.* **1986**, *51*, 3502. (b) For a general review, see: Dipple, A.; Moschel, R. C.; Bigger, C. A. H. *Chemical Carcinogenesis*, 2nd ed.; Searle, C. E., Ed.; ACS Monograph 182, American Chemical Society: Washington, DC, 1984; Vol. 1, pp 41–163.

(2) (a) Flesher, J. W.; Myers, S. R. *Cancer Lett.* **1985**, *26*, 83. See also: (b) Boyland, E.; Sims, P. *Biochem. J.* **1965**, *95*, 780. (c) Dipple, A.; Lawley, P. D.; Brookes, P. *Eur. J. Cancer* **1968**, *4*, 493. (d) Cavalieri, E.; Sinha, D.; Rogan, E. *Polynuclear Aromatic Hydrocarbons: Chemistry and Biological Effects*; Battelle Memorial Institute Fourth International Symposium, Battelle Press: Columbus, OH, 1980; p 214.

(3) (a) Minisci, F.; Citterio, A.; Giordano, C. *Acc. Chem. Res.* **1983**, *16*, 27. (b) Walling, C.; Zhao, C.; El-Taliawi, G. M. *J. Org. Chem.* **1983**, *48*, 4910. (c) Walling, C.; Camainoi, D. M. *J. Am. Chem. Soc.* **1975**, *97*, 1603. (d) Walling, C.; Camaioni, D. M.; Kim, S. S. *J. Am. Chem. Soc.* **1978**, *100*, 4814. (e) Camaioni, D. M.; Franz, J. A. *J. Org. Chem.* **1984**, *49*, 1607. (f) Camaioni, D. M.; Alnajjar, M. S. *J. Org. Chem.* **1985**, *50*, 4456. (g) Dearduff, L. A.; Alnajjar, M. S.; Camaioni, D. M. *J. Org. Chem.* **1986**, *51*, 3686.

(4) Guengerich, F. P.; MacDonald, T. L. *Acc. Chem. Res.* **1984**, *17*, 9.

(5) Sullivan, P. D.; Ocasio, I. J.; Chen, X.; Bannoura, F. *J. Am. Chem. Soc.* **1986**, *108*, 257.

(6) Greene, D. H. *Prog. Phys. Org. Chem.* **1967**, *4*, 135–211.

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proceeded cleanly to give >90% yields of oxidized products with >90% mass balance. In the case of DMA, the single primary product was 9-(hydroxymethyl)-10-methylanthracene (**1**, 31%) as well as the secondary products 9,10-bis(hydroxymethyl)-anthracene (**2**, 43%) and 10-methylanthracene-9-carboxaldehyde (**3**, 21%). Similarly, oxidation of EMA yielded, as a primary product, 9-ethyl-10-(hydroxymethyl)anthracene (**4**, 25%), as well as the secondary oxidation product 10-ethyl-9-anthracene-carboxaldehyde (**5**, 6%). Surprisingly, no 10-methyl-9-(1-hydroxyethyl)anthracene (**6**) was detected. Rather, an unprecedented reaction product, 10-methylanthrone (**7**), was produced in 63% yield (see Figure 2). The relative yield of products was solvent dependent, with the yield of 9-ethyl-10-(hydroxy-methyl)anthracene (**4**) directly proportional to water concentration and dominating the reaction mixture at >20% water (see Table I). Finally, 9,10-diethylanthracene produced 10-ethylanthrone (**8**) only.

The ratio of hydroxymethyl **4** to anthrone product **7** from oxidation of EMA is thus a sensitive function of reaction environment for a common radical cation and provides us with a test for the nature of microsomal oxidation. Indeed, when the oxidation was carried out in a 20% dimethylformamide-water suspension of freshly prepared rat-liver microsomes, hydroxylation to form **4** was observed in only 3% yield, together with an 83% yield of 10-methylanthrone (**7**). In contrast, a cytosol fraction from the same tissue preparation yielded the hydroxylation product **4** in 86% yield along with 9% of anthrone **7**.

Formation of these products is readily interpreted as involving the intermediacy of the dialkylanthracene radical cation, in accord with the recent work of Kochi et al.[7] When a methyl group is present, rapid deprotonation followed by a second one-electron oxidation and hydration of the resulting cation occurs, provided a suitable proton carrier (water) is available. With an ethyl group, stereoelectronic effects inhibit deprotonation. Rather, elimination of ethylene via an unprecedented seven-member transition state appears likely, facilitated by conversion of a benzhydryl radical to an α-hydroxybenzhydryl radical (see Figure 2). In confirmation, ethylene was isolated from the reaction mixture and identified both by mass spectroscopy and trapping with bromine.

The decay of aryalkyl radical cations such as toluene is known to be accelerated in water,[8] a phenomenon we can now directly associate with deprotonation by water acting as a specific base. The paucity of this product of one-electron oxidation in rat-liver microsomes can be attributed to the hydrophobic environment of this oxidative system, a selectivity which is reversed in the (aqueous) cytosolic environment.

Dual pathways involving ring oxidation on the one hand and side-chain oxidation on the other involving a reversibly formed cyclohexadienyl radical have been invoked to explain the divergent oxidation chemistry of methylated benzenes under a variety of conditions.[9] Elimination of ethylene is, we believe, unique to 9-ethylanthracenes and their derivatives, arising as it does from the steric inhibition provided by two peri hydrogens.[10] This result provides a compelling explanation for the enzymic deactivation of 7,12-diethylbenz[*a*]anthracene and 6-ethylbenzo[*a*]pyrene, since the resulting anthrone derivatives are known to be innocuous. It further provides powerful permissive evidence for the intermediacy of radical cations in the biooxidation of these compounds, which, in the hydrophobic microsomal environment, undergo ring oxygenation rather than deprotonation and side-chain oxidation.

Acknowledgment. The preparation of rat-liver microsomes by Lydia C. Fowler and valuable discussions with Dr. Heath Herman and Professor James W. Flesher are gratefully acknowledged.

(7) (a) Schlesener, C. J.; Amatore, C.; Kochi, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7472. (b) Despite the observation of Kochi et al.,[7a] we were able to carry out efficient oxidation in aqueous acetonitrile.

(8) Green, M. M.; Mielke, S. L.; Mukhopadhyay, T. *J. Org. Chem.* **1984**, *49*, 1276.

(9) Walling, C. *Acc. Chem. Res.* **1975**, *8*, 125.

(10) In a related reaction, Dr. Donald Camaioni has observed oxidative elimination of formaldehyde from anthracenemethanol: Camaioni, D. M., Report No. GRI-86/0100, Gas Research Institute, 1986.

Total Synthesis of D- and L-*myo*-Inositol 1,4,5-Trisphosphate

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One of the control mechanisms for regulation of intracellular Ca^{2+} ion concentration involves activation of membrane receptors followed by signal transduction and the release of a modulatory substance.[1] Recent studies[2] provide compelling evidence that activation of these Ca^{2+} mobilizing receptors results in hydrolysis of phosphatidylinositol 4,5-diphosphate, giving rise to D-*myo*-inositol 1,4,5-trisphosphate (IP_3, **1**). IP_3 directly mediates release of intracellular calcium stores. The currently used method for preparing **1** involves chemical hydrolysis of membrane phosphoinositides followed by a tedious purification procedure.[3] Probing the fundamental biochemical processes related to IP_3 requires ready access to **1**, as well as its enantiomer and other derivatives which are not available from natural sources. Furthermore, no radiolabeled derivatives of **1** with high specific activity are currently available. For these reasons, we have developed an efficient chemical synthesis of **1** that may be adapted to the preparation of a variety of phosphorylated inositols and radiolabeled derivatives.

Two general problems impinge on any strategy for the synthesis of polyphosphoinositols. The first is differentiation of the hydroxyl substituents. Phosphorylation of the resultant protected cyclitol in a fashion which allows for efficient deprotection has historically been the second and hitherto unsolved problem.[4] With regard to differentiating the alcohols, a suitably protected triol such as **2** represents a valuable intermediate in the synthesis of **1**. The preparation of such a derivative in racemic form, in which the blocking groups were benzyl ethers, was first reported by Gigg[5] and was accomplished in 10 steps from *myo*-inositol. Ozaki[6] and co-workers have recently reported a synthesis of both enantiomers of triol **2** by a similar route and the conversion of the triol to the antipodes of **1**. In agreement with previous literature,[4] Ozaki et al. found it necessary to employ *N′,N′*-diphenylphosphorodiamidic chloride[7] to effect polyphosphorylation of **2**. This reagent provided a trisphosphoranilide intermediate in about 40% yield. Removal of the six aniline protecting groups required strenuous conditions which resulted in a reportedly poor yield of **1**. We have corroborated the unsatisfactory deprotection of inositol phosphoranilides in prior work in our own laboratory (unpublished data).

We wish to report a practical, eight-step synthesis of both enantiomers of *myo*-inositol 1,4,5-trisphosphate which demonstrates a potentially general solution to the phosphorylation problem and subsequent deprotection. Furthermore, we have developed a considerably shorter and more efficient route to a suitably protected, enantiomerically pure triol similar to **2**.

4-Benzyl-1,2:5,6-di-*O*-cyclohexylidene-*myo*-inositol[8] (**3**) is readily obtained in two steps from commercially available *myo*-inositol by the method of Garegg. Esterification of the free

(1) Somlyo, A. V.; Bond, M.; Somlyo, A. P.; Scarpa, A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5231-5235.

(2) Berridge, M. J.; Irvine, R. F. *Nature (London)* **1984**, *312*, 315-321. Abdel-Latif, A. A. *Pharmacol. Rev.* **1986**, *38*, 227-272 and references cited therein.

(3) Grado, C.; Ballou, C. E. *J. Biol. Chem.* **1961**, *236*, 54-60.

(4) Krylova, V. N.; Gornaeva, N. P.; Oleinik, G. F.; Shvets, V. I. *Zh. Org. Khim.* **1980**, *16*, 315-322. Krylova, V. N.; Lyutik, A. I.; Gornaeva, N. P.; Shvets, V. I. *Zh. Obshch. Khim.* **1980**, *51*, 210-214.

(5) Gigg, J.; Gigg, R.; Payne, S.; Conant, R. *Carbohydr. Res.* **1985**, *140*, c1-c3.

(6) Ozaki, S.; Watanabe, Y.; Ogasawara, T.; Kondo, Y.; Shiotani, N.; Nishi, H.; Matsuki, T. *Tetrahedron Lett.* **1986**, *27*, 3157-3160.

(7) Cremlyn, R. J. W.; Dewhurst, B. B.; Wakeford, D. H. *J. Chem. Soc. C* **1971**, 300-303.

(8) Garegg, P. J.; Iversen, T.; Johansson, R.; Lindberg, B. *Carbohydr. Res.* **1984**, *130*, 322-326.

0002-7863/87/1509-3478$01.50/0 © 1987 American Chemical Society