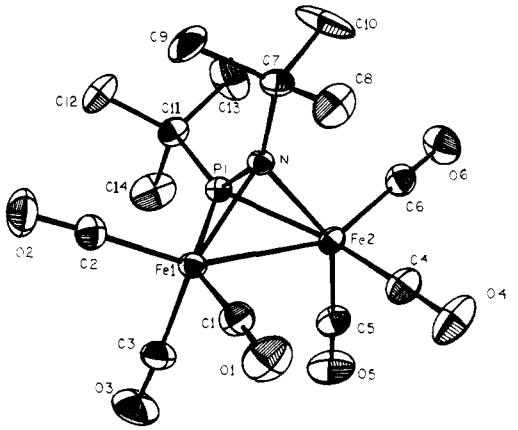


Figure 1. ORTEP view of **1** showing the atom numbering scheme for molecule I. Important parameters: P(1)-N = 1.687 (7), P(1)-Fe(1) = 2.146 (3), P(1)-Fe(2) = 2.147 (3), N-Fe(1) = 2.001 (7), N-Fe(2) = 2.011 (6), Fe(1)-Fe(2) = 2.615 (2) Å; C(11)-P(1)-N = 130.4 (4)°, C(7)-N-P(1) = 139.7 (6)°.

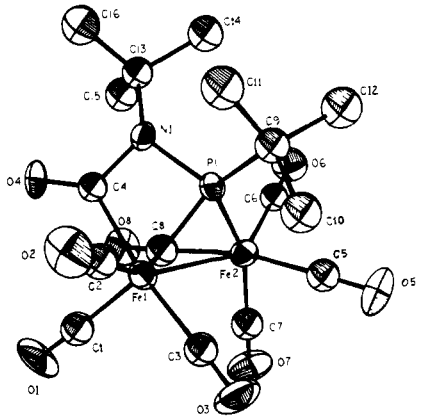
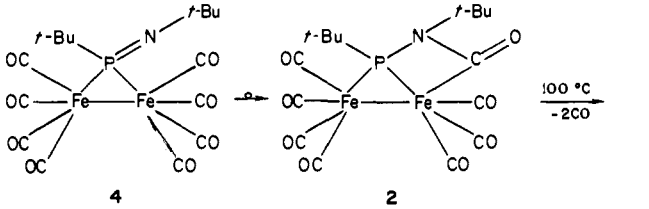


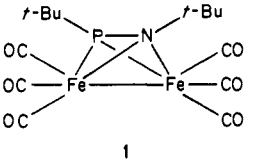
Figure 2. ORTEP view of **2** showing the atom numbering scheme. Important parameters: P(1)-N(1) = 1.729 (10), P(1)-Fe(1) = 2.183 (3), P(1)-Fe(2) = 2.224 (3), Fe(1)-Fe(2) = 2.718 (2), N(1)-C(4) = 1.410 (15), C(4)-Fe(1) = 2.070 (13) Å; Fe(1)-P(1)-Fe(2) = 75.05 (9)°.

diphosphene complex, $(t\text{-Bu}_2\text{P}_2)\text{Fe}_2(\text{CO})_6$ (**3**),[5] **1** was anticipated to feature a phosphorus-nitrogen double bond. However, the P-N bond length for **1** (1.687 (7) Å) corresponds to a bond order of ~1.0. In this respect, **1** resembles analogous R_2N_2 and S_2 complexes.[6] The reason for the retention of the double bond in **3** is therefore not clear.

Compound **2** possesses a novel bicyclic structure (Figure 2).



4 2



1

The long P-N bond in **2** (1.718 (2) Å) is consistent with the slight pyramidality at N(1) (sum of angles = 355.2°).[7] Although we do not know the origin of **2**, we speculate that it arises from **4** via intramolecular nucleophilic attack of the imino nitrogen on a bound CO. The quantitative conversion of **2** to **1** was established by a thermolysis experiment (100 °C, toluene, 30 min). Further studies of the reactivities of **1** and **2** are in progress.

Acknowledgment. We are grateful to the National Science Foundation and the Robert A. Welch Foundation for financial support.

Supplementary Material Available: Tables of bond lengths, bond angles, atomic coordinates, and thermal parameters for **1** and **2** (15 pages). Ordering information is given on any current masthead page.

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Benzene Diol Epoxides

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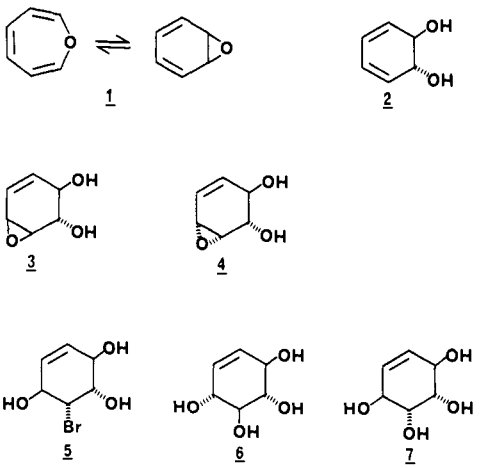
The multistep pathway of metabolic activation of benzene to a species ultimately responsible for the toxic effects ascribed to benzene is not fully understood.[1] Metabolism of benzene proceeds by enzyme-catalyzed oxidation to arene oxide **1** which can undergo



1 2 3 4 5 6 7

spontaneous isomerization to phenol, enzyme-catalyzed addition

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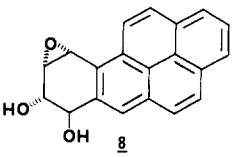
of glutathione, or enzyme-catalyzed hydration to dihydrodiol **2**.[2] Further metabolism of phenol gives *p*-benzoquinone and benzosemiquinone, which have been investigated as active metabolites that bind to biological macromolecules.[3] It appears that enzymatic oxidation of the oxepin valence tautomer of **1** gives muconaldehyde which has been studied as a toxic metabolite of benzene.[4,5]

The role of diol epoxide metabolites as the ultimate carcinogens in the metabolic activation of the carcinogenic polycyclic aromatic hydrocarbons is under detailed investigation. Of the possible diol epoxides derived from polycyclic aromatic hydrocarbons, high mutagenicity and cytotoxicity correlate with structures predicted to be highly reactive according to the "bay region" theory of Jerina and co-workers.[6] Dihydrodiol **2**, by analogy with dihydrodiols derived from polycyclic aromatic hydrocarbons, is a potential substrate for further enzyme-catalyzed oxidation to diol epoxide **3** or **4**. Either could be an activated metabolite responsible for the deleterious effects of benzene. A preparation of **3**, an inhibitor of α-glucosidase from yeast, has been reported, but no physical data were provided.[7,8] The conformation and hydrolytic stability of **3** and **4** have been of interest to theoretical chemists.[9] In view of the importance of **3** and **4** as potential activated metabolites of benzene, we describe below (1) a simple synthesis of **3** and **4** from **2**, (2) the reaction of **3** and **4** with water, and (3) the mutagenicity testing of **3** and **4**. Epoxidation of **2**[10] (*m*-chloroperoxybenzoic acid, Na_2HPO_4, CH_2Cl_2) followed by chromatography (silica gel, ethyl acetate) of the crude reaction mixture without aqueous workup provided **4** (61% yield) as a white, hygroscopic solid (mp 53.5–55 °C) that becomes an oil on exposure to the atmosphere.[11] Reaction of **2** with *N*-bromosuccinimide in aqueous tetrahydrofuran (THF) gave bromide **5** (66% yield).[12] Dehydrobromination of **5** (NaOMe, THF) followed by chromatography (silica gel, 24:1 chloroform–ethanol) gave **3** (62% yield) as a hygroscopic oil.[13] Establishment of the stereochemistry of **5**[12] allows unambiguous assignment of the stereochemistry of **3** and, consequently, **4**. The hydroxyl protons appear as sharp doublets in the ^1H NMR spectrum of **3** (J = 7.5, 11.2 Hz) and **4** (J = 5.3, 6.4 Hz) in $CDCl_3$. The larger coupling constant observed for one hydroxyl proton in **3** supports the prediction of intramolecular hydrogen bonding between the *syn*-hydroxyl group and epoxide oxygen atom of **3** (H–C–O–H dihedral angle 180°) but not **4**.

Solvolysis of **3** and **4** in water at room temperature required several days for complete reaction. Diol epoxide **3** gave **6** (conduritol B)[14–16] in 90% yield and a minor amount (10%) of unidentified material. Diol epoxide **4** gave **7** (conduritol A)[14,17] in 90–95% yield and 5–10% of unidentified material.

Bacterial mutagenesis was measured in the *Salmonella typhimurium* forward mutation assay of Skopek et al.[18] Benzene was not mutagenic at concentrations up to 1000 μg/mL either in the presence or absence of an exogenous metabolising system (PMS).[19] Dihydrodiol **2** required exogenous metabolism (PMS) for mutagenic activity. Diol epoxide **4** was equally mutagenic in the presence and absence of PMS while diol epoxide **3** was inactive with and without PMS. In the forward mutation assay used, **4** was a weak mutagen compared to (±)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (**8**) which has



8

been shown also to be a potent mutagen in the Ames reversion assay (strains TA1538, TA98, and TA100 of *S. typhimurium*).[20] The pattern of mutagenicity observed for benzene, **2**, and **4**, is consistent with the possibility of **4** being a mutagenic benzene metabolite formed via **2**. Because bacterial metabolism may generate additional products from **4**, it remains possible the ultimate mutagen is a further metabolite of **4**.

Acknowledgment. We are grateful to the National Cancer Institute, Training Grant 2 T32 CA 09112, NIEHS Center, Grant P30-ESO-3109, and the National Institutes of Health, Grant GM 26388, for financial support, and to Dr. John C. Dewan for the X-ray crystal structure determination of **5**.

Supplementary Material Available: Experimental procedures, complete spectral data, and analytical data for **3–5** and mutagencity data for **2–4** and representative mutagens, including benzo[*a*]pyrene and **8** (7 pages). Ordering information is given on any current masthead page.

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(11) **4**: ^1H NMR ($CDCl_3$, 270 MHz) δ 5.98–5.89 (m, 2 H, olefinic H), 4.22 (br t, J_{app} = 5.6 Hz, 1 H, carbinol H), 3.83 (t, J_{app} = 6.8 Hz, 1 H, carbinol H), 3.58 (d, J = 5.4 Hz, 1 H, epoxy H), 3.47–3.44 (m, 1 H, epoxy H), 3.23 (d, J = 6.4 Hz, 1 H, OH), 3.07 (d, J = 5.3 Hz, 1 H, OH); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 136.9, 123.0, 73.9, 70.8, 54.7, 50.0.

(12) The stereochemistry of **5** was established by X-ray crystal structure determination.

(13) **3**: ^1H NMR ($CDCl_3$, 270 MHz) δ 6.23 (dd, J = 9.8, 3.9 Hz, 1 H, olefinic H), 6.15–6.08 (m, 1 H, olefinic H), 4.27–4.22 (m, 1 H, carbinol H), 4.01–3.93 (m, 1 H, carbinol H), 3.66–3.63 (m, 1 H, epoxy H), 3.41–3.37 (m, 1 H, epoxy H), 2.42 (d, J = 7.4 Hz, 1 H, OH), 2.26 (d, J = 11.2 Hz, 1 H, OH); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 133.7, 127.8, 68.0, 67.2, 57.3, 47.2.

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(15) **6**: mp 205–206 °C (lit.[14b] mp 204.5–205 °C).

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