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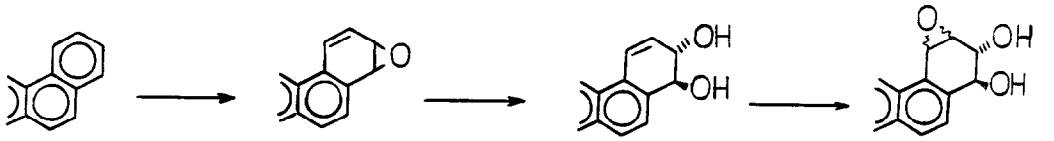
AZA-POLYCYCLIC AROMATIC HYDROCARBON CARCINOGENICITY: PREDICTIONS OF REACTIVITY OF TETRAHYDROBENZO RING EPOXIDE DERIVATIVES

Roland E. Lehr* and Donald M. Jerina+
*Department of Chemistry, University of Oklahoma, Norman, OK 73019
+Laboratory of Bioorganic Chemistry, National Institutes of Health, Bethesda, MD 20205

Abstract: Hückel and perturbational molecular orbital calculations suggest that the position of nitrogen substitution has an important influence on reactivity of tetrahydro-epoxides of aza-polycyclic aromatic hydrocarbons.

In recent years, the focus of polycyclic aromatic hydrocarbons (PAH) carcinogenicity studies has transferred from the parent hydrocarbon to metabolites and potential metabolites of the PAH. For those carcinogenic PAH which have been intensively studied, it now appears that bay region[1] diol epoxides are responsible for a major portion of the tumorigenic activity.[2] These epoxides are formed by three metabolic steps on an angular ring of the PAH:

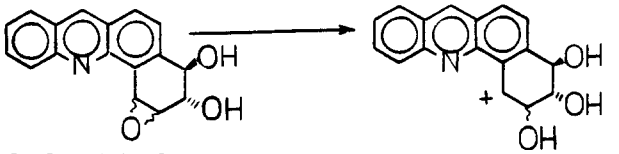


PAH arene oxide dihydrodiol diol epoxide

Diol epoxides with the oxirane ring at a position other than a bay region can also be formed, but they are much less mutagenic and carcinogenic than the bay region diol epoxides.[2] These observations are consistent with perturbational molecular orbital (PMO) predictions of much greater reactivity of the bay region epoxides relative to epoxides at other positions on tetrahydrobenzo rings of PAH, which provided part of the basis for the "bay region theory" of PAH carcinogenesis.[3] Subsequently, numerous other quantum chemical calculations have led to the same conclusion.[4]

Very little is known about the properties of analogous epoxides derived from aza-PAH, although numerous aza-PAH are carcinogens[5] and aza-PAH are known to be environmental contaminants produced by combustion.[6] Systematic experimental studies have begun on the aza-PAH, with an emphasis on benzo-ring derivatives of acridine.[7-10] A theoretical study of methyl-substituted benz[a]- and benz[c]acridines of varying carcinogenicity has been interpreted as consistent with their predicted tendencies toward metabolic activation to bay region diol epoxides[11] but is as yet unsupported by appropriate metabolic studies. We report herein Hückel and PMO calculations on unsubstituted aza-PAH which indicate that the position of nitrogen substitution may have dramatic effects on the reactivity of such epoxides.

As with previous studies of PAH,[3] we have attempted to model epoxide reactivity through calculation of the π-energy change that occurs upon conjugation of a vacant p-orbital at various positions of the aza-PAH. For example, for the conversion of a diol epoxide to a triol carbonium ion:



the π-energy change calculated is for:

Values calculated by the Hückel and PMO methods for the benz- and dibenzacridines are cited in the Table. For the Hückel calculations a value of $\alpha_N = \alpha + 0.5\beta$ was used. For the PMO calculations, the equations used were:

$$\Delta E_\pi = \Delta E_{deloc} \text{ for PAH}^3 \text{ and}$$

$$\Delta E_\pi = \Delta E_{deloc} - 0.5\, a_{0i}^2 \text{ for aza-PAH}^{12}$$

where ΔE_{deloc} is the calculated π-energy change for conversion of the parent hydrocarbon to an arylmethyl cation and a_{0i} is the coefficient in the NBMO of the arylmethyl cation at the same position substituted by nitrogen.

Qualitatively, the predictions of the two methods are similar. In the HMO method, the ΔE_π's for conversion of the aza-PAH to the arylmethyl cation are uniformly lower than for the conversion for the corresponding PAH. However, a major destabilization is calculated only when the plus charge of the arylmethyl cation can be formally conjugated with the nitrogen atom of the aza-PAH, consistent with the higher electronegativity of N relative to C. The same positional dependence is observed in the PMO method, since only when the nitrogen atom is at a "starred" or "active" position in the arylmethyl cation will the coefficient a_{0i} be non-zero. This positional dependence is further shown by the $\Delta\Delta E_\pi$ values, which are equal to the difference in the ΔE_π values between the PAH conversion to arylmethyl cation and that of the corresponding aza-PAH conversion. There is presently a lack of relevant chemical reactivity data to test these predictions. However, a comparison of mutagenicity data for epoxides on angular tetrahydrobenzo rings of benz[a]- and benz[c]acridine epoxides has revealed significant positional effects consistent with the calculated reactivity differences. Thus, while tetrahydroepoxide I is equal to or more mutagenic than the analogous benz[a]-anthracene epoxide toward mammalian and bacterial cells, both II and III (in which the nitrogen atoms are at "starred" positions in the derived benzylic cation) are significantly less mutagenic than the analogous BA epoxides.[13] Further, I is 5 to 12 times as mutagenic as III and the bay region diol epoxides of benz[c]acridine are more than 10 times as mutagenic as the analogous bay region diol epoxides of benz[a]acridine.[13] Studies of dibenzacridine derivatives are in progress.

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SYNTHESIS OF UNSYMMETRICAL 4,4'-DIALKYL-2,2'-BIPYRIDINES

Dean K. Ellison and Reynold T. Iwamoto*
Department of Chemistry, University of Kansas
Lawrence, Kansas 66045

Summary: Conversion of 4,4'-dimethyl-2,2'-bipyridine to 4-hexadecyl-4'-methyl-2,2'-bipyridine, 4-heptadecyl-4'-methyl-2,2'-bipyridine, and 4,4'-diheptadecyl-2,2'-bipyridine by treatment with lithium diisopropylamine followed by an appropriate alkyl bromide is reported.

Numerous recent studies of ruthenium bipyridine complexes of the type $Rubipy_2L^{2+}$ where bipy is 2,2'-bipyridine and L is 4-alkyl-4'-methyl-2,2'-bipyridine or 4,4'-dialkyl-2,2'-bipyridine as sensitizers in the photocatalytic cleavage of water[1-6] have called attention to the complexity of the synthesis of unsymmetric 4,4'-dialkyl-2,2'-bipyridine, as well as that of the symmetric analogs.[1-7] This latter situation has led to extensive use in these studies[1-6] of $Rubipy_2L^{2+}$ complexes with symmetrical 4,4'-dialkyl-2,2'-bipyridines for ligand L in spite of the fact that the complexes with unsymmetrical 4-alkyl-4'-methyl-2,2'-bipyridines for L have been shown to improve drastically the photocatalytic cleavage of water.[1] Reported here is a particularly simple method for the synthesis of unsymmetrical 4-alkyl-4'-methyl-2,2'-bipyridines and symmetrical 4,4'-dialkyl-2,2'-bipyridines in which one or both of the $-CH_3$ groups on 4,4'-dimethyl-2,2'-bipyridine are converted with lithium diisopropylamine to $-CH_2^-$ anionic groups, and the latter subsequently caused to react with alkyl bromides to place long alkyl groups in the 4- or 4,4'- positions.

For the preparation of the unsymmetrical bipyridines, 50 mL of tetrahydrofuran containing 9.2 mmoles (1.69 g) of 4,4'-dimethyl-2,2'-bipyridine (prepared according to Ghosh and Spiro[8]) was added dropwise over a 30 min period to 4.1 mL of a tetrahydrofuran solution containing 9.1 mmoles of lithium diisopropylamine. (The lithium diisopropylamine solution was prepared by the treatment of a mixture of 1.4 mL diisopropylamine and 2.7 mL tetrahydrofuran with 6.4 mL of 1.42 M butyllithium. The resulting mixture was stirred for 15 min under dry argon before the addition of the bipyridine.) After the orange-brown solution was stirred for 1.5 hr, it was cooled to 0° and 9.2 mmoles of n-hexadecyl bromide or n-pentadecyl bromide was added dropwise while stirring was maintained. After 1.5 hr, during which time the solution turned turbid, the reaction was quenched with ice water and the mixture extracted with ether. The residue after removal of ether was recrystallized three times from ethyl acetate to provide the pure product in 60-70% yield.[9]

For the preparation of the symmetrical 4,4'-diheptadecyl-2,2'-bipyridine, the mmoles of lithium diisopropylamine and of n-hexadecylbromide were doubled.

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9. The two unsymmetrical 4,4'-dialkyl-2.2'-bipyridines were characterized by melting point, elemental analysis, and NMR. All the information obtained for 4-hexadecyl-4'-methyl-2,2'-bipyridine agreed excellently with those reported earlier by Johansen et al.[2] for the same compound prepared by a different procedure.

   a. 4-Hexadecyl-4'-methyl-2,2'-bipyridine: M.p. 62-63°; $C_{27}H_{42}N_2$; C, 82.17; H, 10.73; N, 7.10. Found C, 81.94; H, 10.85; N, 6.94. NMR (80 MHz, $CDCl_3$, TMS) δ 0.65-1.95 (multiplet, $C_{15}H_{31}$, 2.41(3H, s, 4'-Me), 2.69 (2H, t, CH_2), 7.10 (2H, d, H5, H5') 8.24(2H, s, H3, H3') 8.53(2H, d, H6, H6').

   b. 4-Heptadecyl-4'-methyl-2,2'-bipyridine: M.p. 73-74°; $C_{28}H_{44}N_2$; C, 82.29; H, 10.85; N, 6.85. Found C, 82.10; H, 10.90; N, 6.80. The NMR spectrum is identical with that of 4a, except for a 33 H multiplet at 0.7-1.95.

   c. 4,4'-Diheptadecyl-2,2'-bipyridine: Although not formally characterized, the NMR spectrum of this compound was similar to that of 4a, except for the absence of the signal at δ 2.39, 4'-Me. The molecular weight of this bipyridine was confirmed by mass spectrometry.

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