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INDUCED NUCLEOPHILIC SUBSTITUTION BENZO[a]PYRENE

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Induced Nucleophilic Substitution in Benzo[a]pyrene

Cavalieri and Calvin have proposed[1,2] that the carcinogenic action of benzo[a]pyrene (BaP) may arise from aryl hydroxylase induced binding to nucleophilic cellular components. The theory proposes that attack by electrophilic oxygen, produced in the hydroxylase system, occurs at the 6 position of the hydrocarbon to give a carbonium ion, localized primarily at the 1 and 3 positions, which can undergo attack with nucleophilic cellular components. Alternatively, initial attack could occur at 1 or 3, followed by nucleophilic reaction at 6.

Some evidence for the theory has been obtained by using iodonium ion as a model for the hydroxylase system. Benzo[a]pyrene and iodine dipyridine nitrate react to give either the 6-iodo or 6-pyridinium derivative or a mixture depending upon reaction conditions. Effects of solvent, concentrations and ratios of reactants were investigated and are summarized in the following table. Equimolar quantities of the reagents react within ten minutes in chloroform to give 6-iodobenzo[a]pyrene in nearly quantitative yield. All other reactions listed require up to 24 hours to reach completion. Formation of the pyridinium derivative requires a 2:1 molar ratio of iodonium reagent to BaP.

Effect of Reaction Variables on Product Formation

Concentration of BaP	Molar Ratios py/BaP*	Molar Ratios (py-I-py)**/BaP	Solvent	Yield, % I-BaP	Yield, % py-BaP
		1	$CHCl_3$	99	trace
		1	MeOH	95	
		1	DMF	95	
			pyridine	no reaction	
1 mg/ml	32	2	1% py/$CHCl_3$	50**	50**
0.5 mg/ml	64	2	"		95
5 mg/ml	30	2	5% py/$CHCl_3$		95
"	30	1	"		50
1 mg/ml		2	CH_3CN		10

* added pyridine

** approximate yields

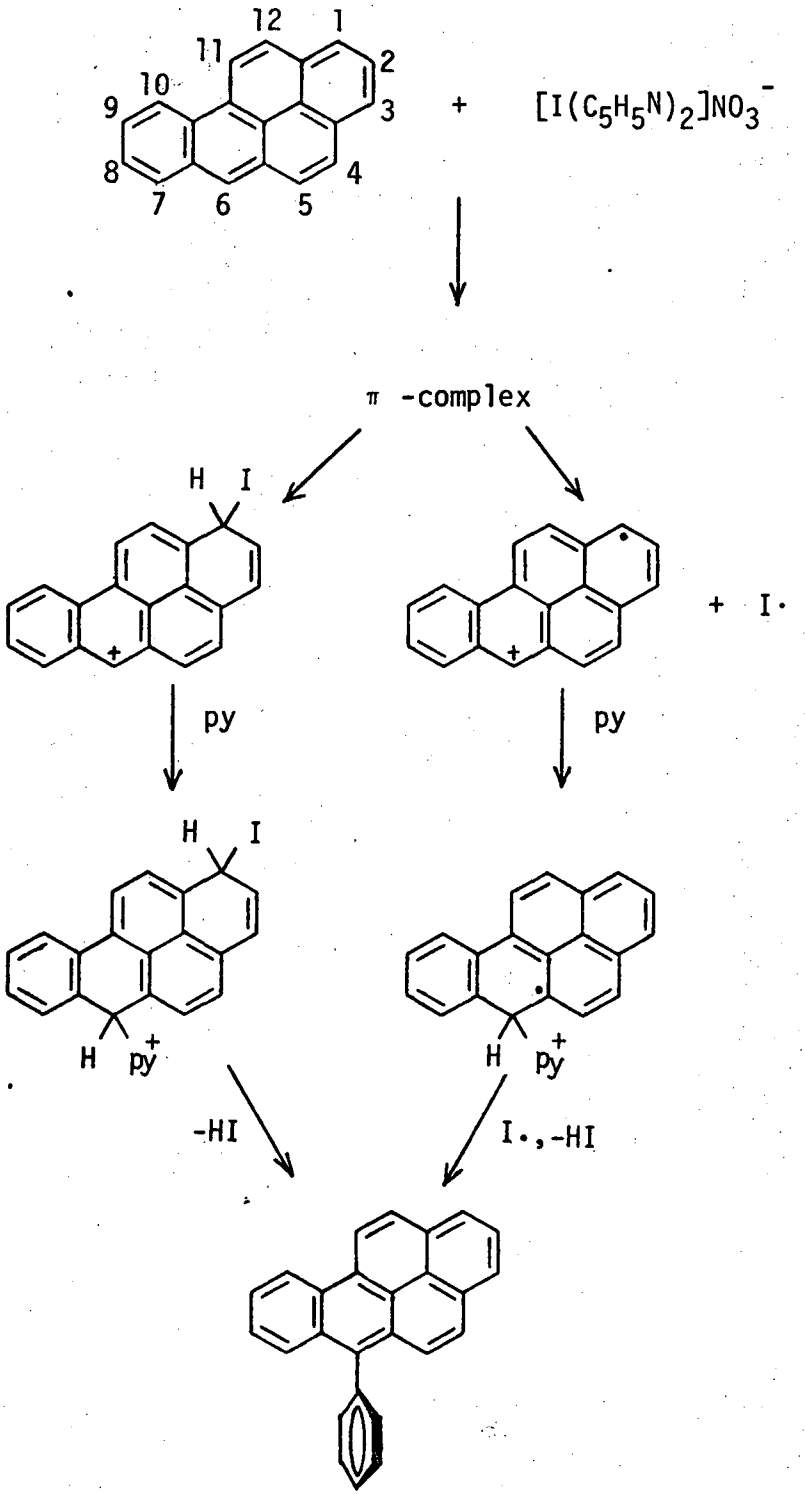
The formation of the 6-pyridinium derivative may be interpreted as arising via the proposed ionic mechanism with initial electrophilic attack occurring at position 1 or 3 rather than at position 6 as occurs in the formation of 6-iodobenzo[a]pyrene. The position of attack might change for steric reasons since different reagents could be involved as indicated by the following equilibria:

$$(py\text{-}I\text{-}py)^+ \rightleftharpoons (py\text{-}I)^+ + py \rightleftharpoons I^+ + 2\ py$$

If formation of 6-iodobenzo[a]pyrene arises from attack by I^+, the equilibrium in pyridine-chloroform will be displaced to the left and a bulkier reagent might attack at position 1 or 3 to result in formation of the 6-pyridinium derivative. Steric factors are important since acylation with succinic anhydride and aluminum chloride gives the product with substitution in the one position.[4] The excess pyridine present in the reaction mixture may also provide conditions where the addition of pyridine to the sigma complex formed by electrophilic attack at 1 or 3 is faster than the rate of elimination of a proton which would give the 1- or 3-iodo derivative. The dihydro-disubstituted compound thus formed would then undergo elimination of HI to give the 6-pyridinium derivative.

The reaction can also be postulated to proceed via the radical cation of BaP. Although evidence has been found[3] that the radical cation of BaP, produced by oxidation with iodine, reacts with pyridine to give the 6-pyridinium derivative, no radical was detected under the conditions of these reactions. The simple iodine reaction does not proceed under the conditions employed in this study.

Both the ionic and radical modes are shown in the following reaction scheme.



The structural assignments for the iodo and pyridinium derivatives are based on the ultraviolet and 220 MHz nuclear magnetic resonance spectra. The UV spectra match reported spectra for 6-iodobenzo[a]pyrene[5] and 6-pyridinium benzo[a]pyrene perchlorate.[3] The NMR assignments are based on comparison with the spectrum of the parent hydrocarbon[6,7], coupling constants, splitting patterns, and double resonance decoupling experiments. The NMR spectra of the pyridinium derivative establishes the fact that the plane of the pyridine ring is perpendicular to the plane fo the benzo[a]-pyrene ring since protons 5 and 7 are shielded, relative to their positions in the parent compound, by the pyridine ring current. This is in contrast to the deshielding which all the protons, including 5 and 7, exhibit in the 6-iodo compound.

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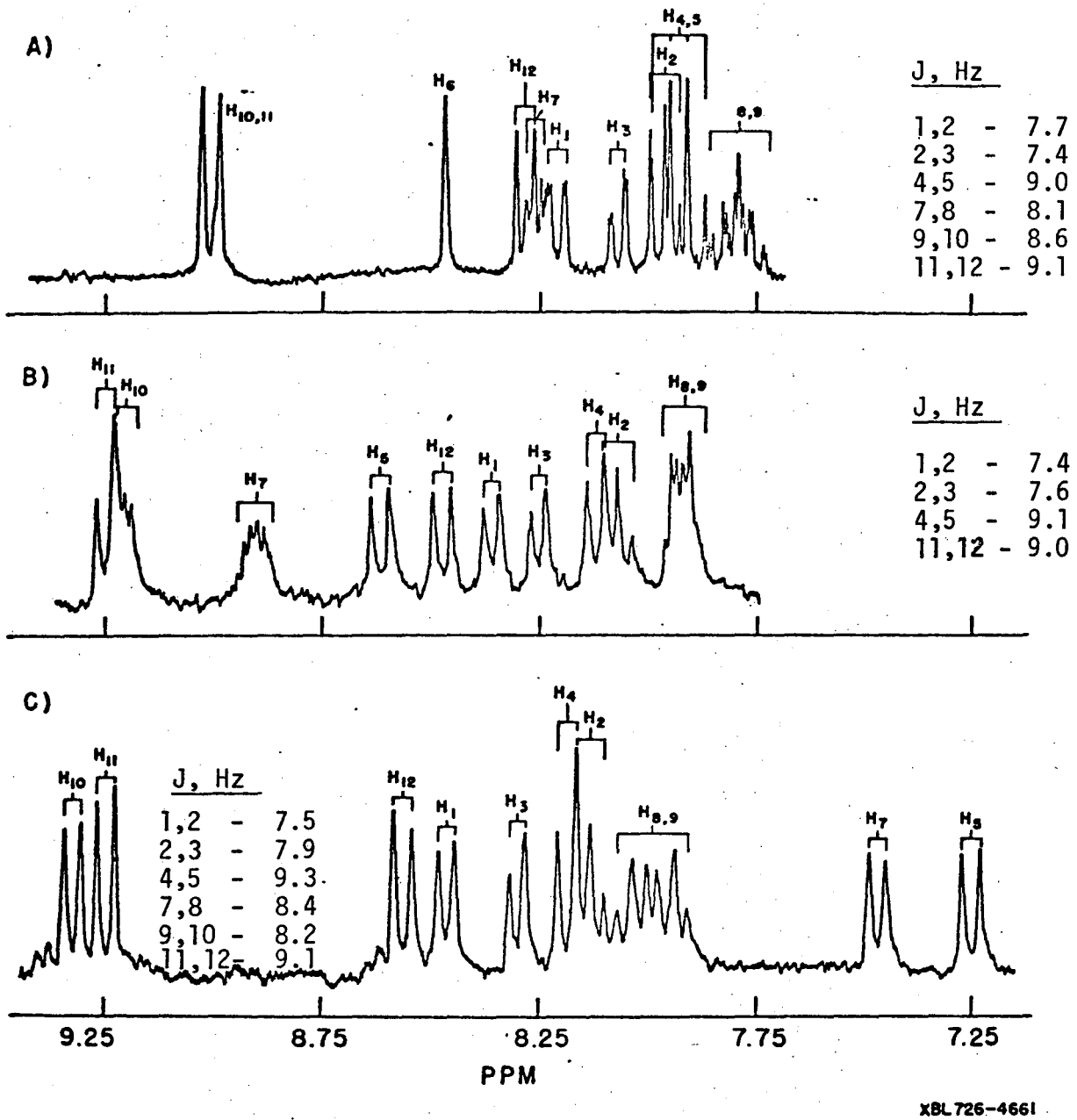

The 220 MHz NMR spectra of A. Benzo[a]pyrene in $CDCl_3$, B, 6-iodobenzo[a]pyrene in tetrahydrofuran, and C. the 6-pyridinium-d_5 derivative of benzo[a]pyrene in methanol.

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