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ON THE POTENTIAL CARCINOGENIC AND MUTAGENIC CHARACTER OF BENZOBIPHENYLENES

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Abstract: PMO estimations suggest certain partially saturated benzobiphenylene carbonium ions might exhibit carcinogenic and/or mutagenic activity.

It has been proposed that one of the principal structural features favoring carcinogenic and mutagenic activity of the metabolites from polycyclic aromatic hydrocarbons (PAH's) is an oxirane ring in a saturated, angular benzo-ring that forms part of a "bay region" of the parent PAH[1]. Of several possible isomeric arene oxides, it has been suggested[1] that perturbation molecular orbital (PMO) calculations[2] of the change in π-electron delocalization energy upon the opening of a benzylic C-O oxirane bond to yield a carbonium ion can be used to identify the potentially most carcinogenic member(s). This change of the π-electronic system from N to N+1 centers while the number of electrons remains the same can be estimated for alternate PAH systems by the following simple formula: $\Delta E_{deloc.} = 2(1-\underline{c})\beta_0$, where $\underline{c}$ is the coefficient of the nonbonded molecular orbital of the carbonium ion and β_0 is the benzene carbon-carbon $2p_z$-$2p_z$ resonance integral[2]. The $\underline{c}$ may be calculated by a very simple pencil and paper procedure that is well known[2]. Greater values for the $\Delta E_{deloc.}$ are taken to indicate a greater tendency for the oxirane to undergo ring opening towards a carbonium ion intermediate that ultimately may be captured by attack by some nucleophilic functional group of a biopolymer. This description of the carcinogenic potential of various microsomal monooxygenase metabolites of the PAH's benz[a]anthracene and benz[a]pyrene has been extensively discussed by Jerina et al.[1,3] and the general prediction that carbonium ion character may play a significant role in the mechanism of PAH metabolite carcinogenicity has been discussed by Hulbert[4]. PMO estimations also predict a number of potential "non-bay region" metabolites of PAH's that may yield carbonium ions possessing stabilities similar or greater than those of "bay region" metabolites of carcinogenic PAH's. Some cases have already been noted where "non-bay region" carbonium ions are estimated by the PMO method to possess greater $\Delta E_{deloc.}$ than a related "bay region" one but metabolic and mutagenic testing indicates the former species lack significant metabolic involvement and activity[1,3]. Recently several pieces of evidence have been presented which indicated that "non-bay region" metabolites can be significantly mutagenic[5,6]. Thus, the detailed relation between "bay region" and

"non-bay region" carbonium ion reactivity and biological activity requires much additional study but, as a first approximation, carbonium ion stabilities should be kept in mind.

In the process of considering how various electronic features of PAH's might affect their carcinogenic potential, we have had occasion to use the PMO approach to study a wide variety of PAH carbonium ion systems. One structural feature whose effect we have looked at has been the introduction of a sp^2 hybridized, four-membered ring into PAH systems. This structural feature is a part of a number of stable biphenylene derivatives that have been known for some time[7-14]. $\Delta E_{deloc.}$ predictions by the PMO approximation for these systems may be significant and suggest that due caution be exercised when working with various members of this class of compounds. Figure 1 summarizes our results.

Of the systems shown in Figure 1, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13 are predicted to possess one or more carbonium ions exhibiting a $\Delta E_{deloc.}$ similar to or greater than those for known carcinogenic and mutagenic systems. Whether the parent PAH's of these substances are substrates for the liver monooxygenase-epoxide hydratase system[15,16] is not known at present. For comparison the following carcinogenic and/or mutagenic systems possess the listed $\Delta E_{deloc.}$ in units of β_0 for their most stable carbonium ion from a tetrahydro-benzo- ring derivative: benzo[g]chrysene, 0.728; dibenz[a,h]anthracene, 0.738; benz[a]anthracene, 0.766; dibenz[a,e]pyrene, 0.778; and benz[a]pyrene, 0.794[3]. The systems 7, 8, 9, 11, 12, and 13 all possess "non-bay region" carbonium ions with significant $\Delta E_{deloc.}$. In view of the synthesis of the parent PAH of 10[13] and a close relative of 13[14] and the significant $\Delta E_{deloc.}$ for 10, 11, 12, and 13, great caution should be exercised when working with these and related systems.

Rather detailed studies have been reported dealing with the identification and quantitation of PAH's arising from combustion processes and present in the environment[17-23]. Multitudes of compounds have been identified by gas chromatography and mass spectroscopy but there are still many unidentified species. No consideration appears yet to have been given to the possibility that biphenylene and benzobiphenylenes might arise in these samples[17-23]. In view of the predictions given here, this possibility should be investigated. This possibility is not inconsistent with mechanisms discussed for formation of PAH's in combustion processes[17,18].

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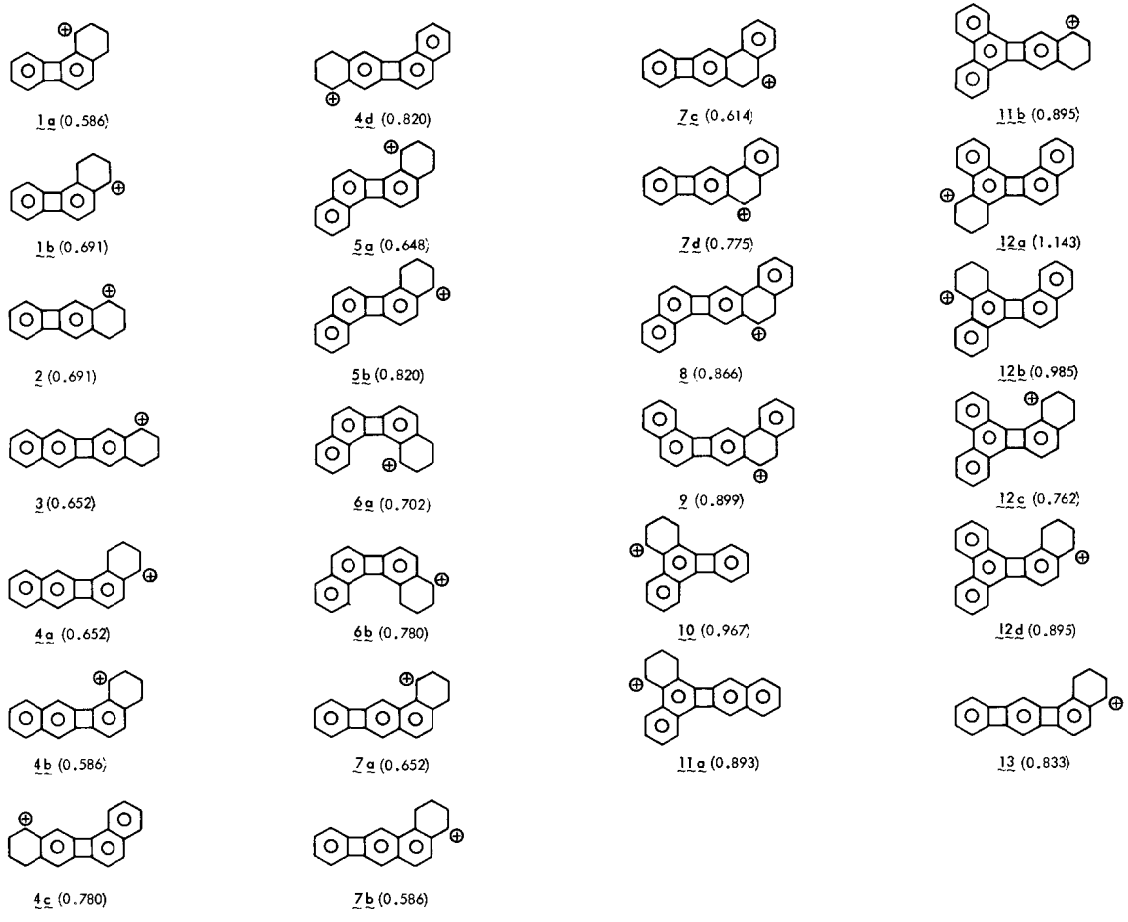

Figure 1. PMO ΔE_{deloc}'s (in units of β_0) for Formation of Various Carbonium Ions

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