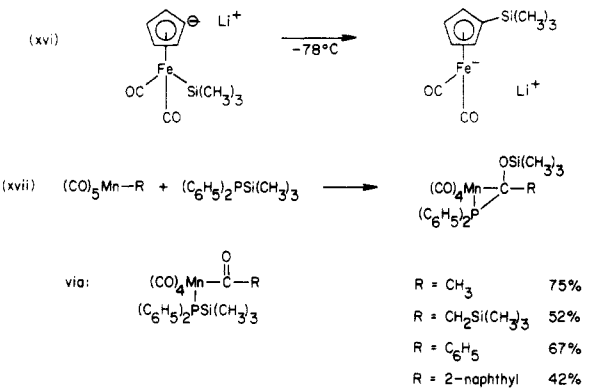
early transition metal[41] and coordinatively unsaturated[5] trialkylsilane complexes.

Mechanisticaly, we are coming to the realization that diverse types of organosilicon reactivity modes can manifest themselves within the coordination sphere of a transition metal. Striking examples include the silatropic shifts noted above and the Brook-like rearrangement (eq xvi) discovered by Berryhill.[42] Such reactions will be increasingly sought and exploited by synthetic organometallic and inorganic chemists. As an illustration, consider the recently reported $(C_6H_5)_2PSi(CH_3)_3$-induced CO insertion and cyclization shown in eq xvii.[43] We hope that this account has provided its readers with a firm basis for the rational design of such chemistry.



I express my sincere thanks to the research associates who collaborated on this project: Dennis L. Johnson, Dr. Andrew J. Blakeney, Kerry C. Brinkman, Marianne Marsi, Wilfried Krone-Schmidt, Patrick Donovan, George D. Vaughn, Dr. Hiroshi Nakazawa, Bill D. Zwick, K. Alex Krein, and Carol A. Lisensky. The National Science Foundation is gratefully acknowledged for suport of this research.

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Predicting Carcinogenicity of Polycyclic Aromatic Hydrocarbons

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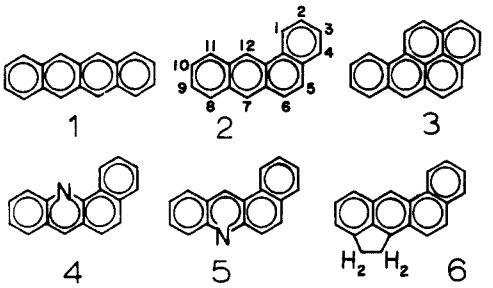
Polycyclic aromatic hydrocarbons (PAH) and related molecules display a wide range in cancer-inducing activity.[1] For instance, **1** is not carcinogenic, **2** is weakly carcinogenic, and **3** is very carcinogenic. **2** can be made much more carcinogenic by methylating position 6, 7, or 12, but methylation in any of the positions 1–5 causes complete loss of activity. Replacing a C–H in **2** by nitrogen to give **4** or **5** removes carcinogenic activity, but **4** can be more easily reactivated by methylation than can **5**. **6** is extremely carcinogenic.



Why do these structural modifications cause these changes in carcinogenicity? Chemists have been intrigued by this question since such data began to become available in the 1930s. Physical properties, such as lipophilicity[2] and molecular shape,[3] appear to play a role, but these can only be expected to distinguish between molecules that differ in major ways. There must be other factors too, presumably having to do with chemical reactivity, and it is on these that chemists have focused their attention. In most cases, quantum chemical calculations have been used to generate re-

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(1) (a) Arcos, J. C.; Argus, M. F. "Chemical Induction of Cancer"; Academic Press: New York, 1974 (b) Dipple, A. In "Chemical Carcinogens"; Searle, C. E., Ed.; American Chemical Society: New York, 1976; pp 245–314. (c) Berenblum, I. In "Physico-Chemical Mechanisms of Carcinogenesis" (The Jersalem Symposia on Quantum Chemistry and Biochemistry); Academic Press: New York, 1969; Vol. 1, pp 321–324.
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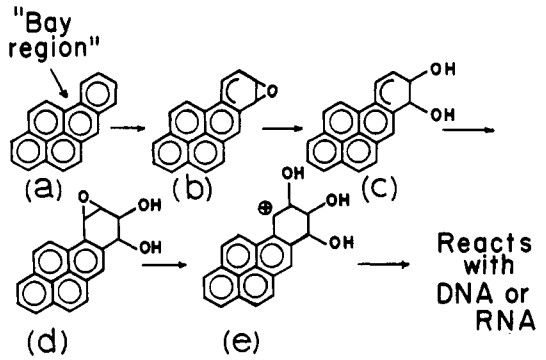
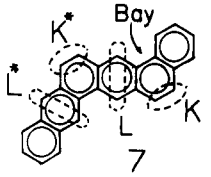


Figure 1. Benzo[*a*]pyrene (a) forms, in succession, an epoxide (b), a dihydrodiol (c) ("proximate carcinogen"), a dihydrodiol-epoxide (d) ("ultimate carcinogen"), and an unstable triol carbocation intermediate (e), which reacts with DNA or RNA.

activity indexes for PAH or related molecules, and correlations have been sought between these indices and carcinogenicity.

Until recently, the most widely known MO-based indices to correlate with carcinogenicity were the K- and L-region indices proposed by A. Pullman in 1945 and developed into a more extended theory with B. Pullman.[4] A K region is defined as the external corner of a phenanthrenic moiety in a PAH, whereas an L region consists of a pair of opposed, open anthracenic "point" atoms. Compound **7** has two K and two L regions, with

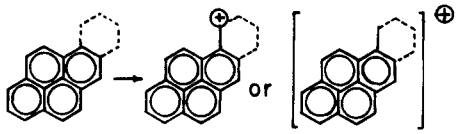


MO calculations indicating that the asterisked positions are most reactive. If the more reactive K region exceeds a certain reactivity limit, carcinogenicity is expected unless the more active L region also exceeds *its* reactivity limit. In this case the molecule is expected to be inactive. In **7**, K* is sufficiently reactive for carcinogenicity, but L* suffices to "turn off" the molecule, so **7** is predicted to be noncarcinogenic.[4c] A possible explanation is that an active L region is involved in reactions that prevent the K region from initiating cancer.

These indicators were developed at a time when very little was known about what actually occurs between the exposure of an organism to a PAH and the occurrence of cancer. Since then, great progress has been made.[5] Benzo[*a*]pyrene (BP), **3**, has been the most thoroughly studied, and the sequence of enzyme-assisted chemical transformations thought to lead to the induction of tumorigenesis is shown in Figure 1. Recognition that the diol-epoxide (d) of benzo[*a*]pyrene is the "ultimate carcinogen" of this PAH has provided important direction for understanding the wide range of tumor-initiating activity of different PAH. In particular, Jerina and co-workers[6a] have shown that a correlation exists between observed PAH tumorigenicity and computed ease of going from the diol-epoxide (d) to the triol-carbocation form (e).[7] The first calculations[6a-d] were π-electron calculations of the simplest kind, but more sophisticated all-valence-electron calculations[6e] showed similar trends. The implication of this correlation—that the tumorigenicity induced by a PAH is predominantly controlled by the ease with which the diol-epoxide derivative forms a triol-carbocation-like intermediate—has been subsequently shown to be an oversimplification.[7] For example, a number of PAHs are inhibited from becoming metabolized to proximate diols or ultimate diol-epoxides. Certain stereochemical features are also of importance in the induction of tumorigenesis. Many of these exceptions are, however, understood, and calculated ease of carbocation formation has continued to serve as a guiding concept for many experimental and theoretical research projects.

In this Account we review studies of PAH carbocation stabilization and demonstrate how the predictive capabilities that have been developed can be distilled into a few rules and techniques that do not require use of a computer. This allows one to quickly estimate relative diol-epoxide reactivities of relevant PAH.

Since π-only and all-valence calculations broadly agree, the relative ease of triol-carbocation formation must be controlled by π-electron energetics in most cases. This means that the theoretical idealization for the process d to e of Figure 1 is **8** to **9**. (The dashed



8 **9** **9′**

line refers to the saturated part of the molecule, which is not part of the π system.) In essence a carbocationic "branch" is added to a neutral, conjugated portion of the original PAH. We model this by imagining that a CH_2^+ group has been attached to the π system. **9′** and **9** represent the same carbocation, with **9′** emphasizing the fact that the positive charge is delocalized over the entire π system.[9]

Note that the more active diol-epoxide form of benzo[*a*]pyrene is as shown in Figure 1d and not as shown in **10**. Quantum chemical calculations indicate that, even if **10** is formed, it should have greater difficulty

(4) (a) Pullman, A. *C. R. Hebd. Seances Acad. Sci.* **1945**, *221*, 140. (b) Pullman, A. *C. R. Seances Soc. Biol. Ses Fil.* **1945**, *139*, 1056. (c) Pullman, A. *Bull. Soc. Chim. Fr.* **1954**, 595–603. (d) Pullman, A.; Pullman, B. *Adv. Cancer Res.* **1955**, *3*, 117.

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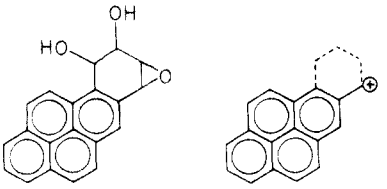
(8) Pullman, B. *Int. J. Quantum Chem.* **1979**, *16*, 669–689.

(9) (a) Streitwieser, A., Jr., "Molecular Theory for Organic Chemists"; Wiley: New York, 1961. (b) Dewar, M. J. S. "The Molecular Orbital Theory of Organic Chemistry"; McGraw-Hill: New York, 1969.

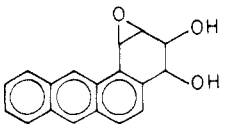
(10) The "reverse" BP diol-epoxide **10** has been found to bind significantly to DNA in vitro. However, the observed binding is apparently intercalative and not covalent. See: Macleod, M. C.; Selkirk, J. K. *Carcinogenesis* **1982**, *3*, 287–292.

in forming the corresponding triol–carbocation **11**. In short, **9** is a more stable carbocation than is **11**. This comes about because the π electrons of the pyrene moiety delocalized onto the added CH_2^+-like branch more in **9** than in **11**.[9]



10 11

Jerina and co-workers[6a,11] noticed that experimentally more active diol–epoxides are associated with a particular structural feature called a "bay region", defined as an open *inner* corner of a phenanthrenic moiety. One of the ends of the phenanthrenic moiety must be a terminal ring of the PAH. Thus, **7** has two inner corners, but only one of them is a bay region. Jerina et al.[6a-c] observed that the diol–expoxides which are computed to lead most easily to triol–carbocations have the epoxide in the bay region. **10** is not a bay-region diol–epoxide because the epoxide group is on the side of the terminal ring away from the bay. Benz[*a*]-anthracene, **2**, has four possible terminal ring diol–epoxides (ignoring detailed stereochemical differences) because it has two terminal rings. The bay-region theory states that, of these, **12** should form the triol–carbocation most easily.



12

Once a preferred site for the carbocationic branch has been recognized, namely, the bay-region site, we can ask how the stability of the carbocation changes if we do such things as (a) modify the ring structure elsewhere in the system by adding, removing, or rearranging rings, (b) methylate, fluorinate, or otherwise substitute for hydrogen, (c) replace carbons with other elements, like nitrogen, and (d) include five-membered rings in the structure. Numerous quantum chemical calculations have been performed in order to follow the effects of such modifications.[6,12-14] The results are generally in agreement with observed carcinogenicities.[1,15]

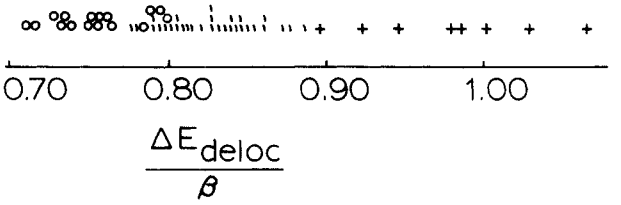


Figure 2. π-Delocalization energy (in units of β) for CH_2^+ substitution at various sites on ten PAH molecules. Greater delocalization energy corresponds to greater ion stability. +, |, O refer respectively to CH_2^+ attachment to α', α, or β sites.

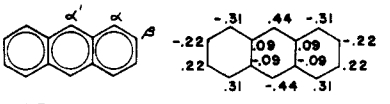
A major thrust of our own research has been to understand the reasons for the results of such computations. This has led to recognition of the aforementioned simple rules and techniques.

Why Are Bay-Region Ions More Stable?

The answer[16] to this question is that bay-region ions place the CH_2^+ branch on an α-position of the PAH fragment, where α means one bond removed from a fusion site. All other possibilities for carbocationic branch placement via reaction of a *terminal* ring turn out to be β-positions—two bonds away from a fusion site. The bay-region theory amounts to the statement that α sites stabilize a cationic branch better than β sites.[16]

The superiority in naphthalene of an α over a β site for stabilizing a positive branch, as well as for nucleophilic and radical processes, has been recognized for many years.[17] We have shown this to be generally true[16] by comparing calculated carbocation stabilities over a large number of positions on several PAH (Figure 2). When we include α'-positions—sites one bond removed from *two* fusion sites—we find them to be best of all for stabilizing a carbocationic branch. Since there is no way a *terminal* six-membered ring can be connected to an α' site, such sites are not relevant to the question of carcinogenicity induced by alternant PAH. However, as we shall see in the next section, they can be involved in the carcinogenicity induced by nonalternant PAH (i.e., PAH with odd-membered rings).

The three different types of position are illustrated for anthracene, **13**. It is well-known that the α' sites of anthracene are the most reactive,[17] but we are not aware of this having been recognized to be true of α' sites in general.



13 14

Why the Site Order $\alpha' > \alpha > \beta$?

The stabilization energy is dominated by the interaction between the highest occupied MO's (HOMO's) of the PAH fragment and the empty π atomic orbital (AO) on the "branch" atom;[16] wherever the HOMO is of greatest absolute size, the interaction with the branch will be greatest. The HOMO of anthracene, **14**, is

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(14) (a) Perin-Roussel, O.; Croisy-Delcey, M.; Mispelter, J.; Saguem, S.; Chalvet, O.; Ekert, B.; Fouquet, J.; Jacquignon, P.; Lhoste, J.-M.; Muel, B.; Zajdela, F. E. *Cancer Res.* **1980**, *40*, 1742–1749. (b) Lowe, J. P.; Silverman, B. D. *J. Am. Chem. Soc.* **1984**, *106*, 0000–0000. (c) Fu, P. F.; Beland, F. A.; Yang, S. K. *Carcinogenesis* **1980**, *1*, 725–727. (d) Rastetter, W. H.; Nachbar, R. B., Jr.; Russo-Rodriguez, S.; Wattley, R. V.; Thilly, W. G.; Andon, B. M.; Jorgensen, W. L.; Ibrahim, M. *J. Org. Chem.* **1982**, *47*, 4873–4877. (e) Boyd, D. E.; Stubbs, M. E. *J. Am. Chem. Soc.* **1983**, *105*, 2554–2559.

(15) Wood, A. W.; Chang, R. L.; Levin, W.; Ryan, D. E.; Thomas, P. E.; Lehr, R. E.; Subodh, K.; Schaefer-Ridder, M.; Englehardt, U.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1983**, *43*, 1656–1662.

(16) Lowe, J. P.; Silverman, B. D. *J. Am. Chem. Soc.* **1981**, *103*, 2852–2855.

(17) Roberts, J. D.; Caserio, M. C. "Modern Organic Chemistry"; W. A. Benjamin: New York, 1967; pp 560–562.

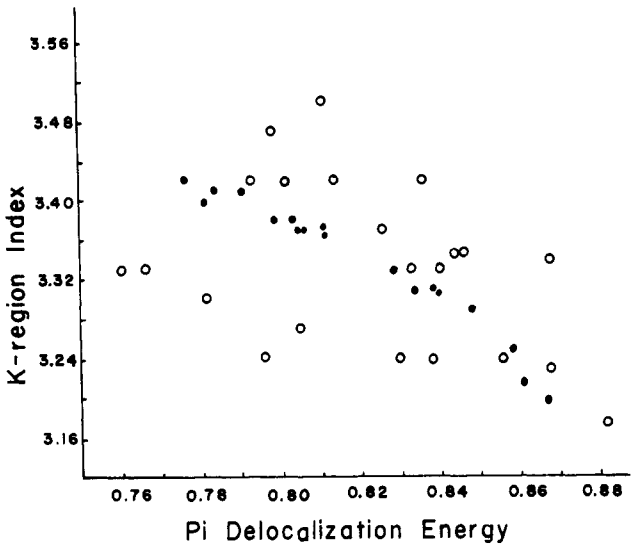
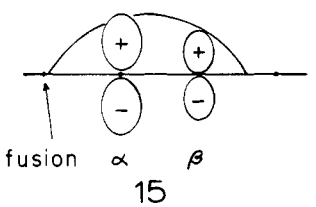


Figure 3. K-region index vs. Hückel delocalization energy, both in units of β, for various PAHs. Solid circles are for primitive K regions and hollow circles for nonprimitives.

largest (absolutely) at the α'-positions, next largest at α-positions, smaller at β-positions, and nearly zero at the fusion sites. Sometimes, if the shape of the PAH fragment is more complicated, the HOMO is prevented from showing this behavior, but then we find several high-energy occupied MOs that, collectively, still put more high-energy electronic charge at α' than at α, etc.

The explanation[16] of why the HOMO has its largest coefficients at α'-positions, next largest at α, etc. has two parts. The first has to do with placement of the nodes of the HOMO. We can tell, from inspecting **14**, that the nodes in the HOMO are near fusion-site carbons. There is a reason for this. Fusion carbons can bond with *three* neighbors, and we find that the lowest energy occupied MO's tend to be largest at fusion sites because this maximizes the bonding. Indeed, that is what gives these MO's their low energy. By the time we get to the HOMO, the ability of the fusion sites to participate in an MO has been pretty well used up, so we find small coefficients there, which means that the fusion sites are near a node. The second part of the explanation has to do with the wavelength of the HOMO. The energy of the HOMO of our PAH fragment is typically about 0.5 β below the nonbonding energy, in simple Hückel terminology. This means that the distance between nodes is slightly longer than the distance of two C–C bonds that characterizes nonbonding MO's. Typically, it is about two and one-half C–C bonds. Now, if we know that a HOMO node occurs near a fusion site and that the next node occurs about two and one-half C–C bonds from there, it follows immediately that the HOMO is bigger at an α-carbon than at a β-carbon, as indicated in **15**. An α' site is especially favored.[16]

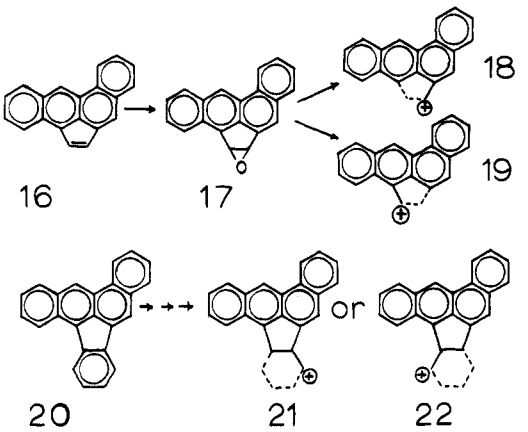


15

The above chain of reasoning has connected the observation that bay-region ions are especially stable to the basic nature of the one-electron method in quantum chemistry. As a practical matter, it is best simply to remember that, *in general*, $\alpha' > \alpha > \beta$ *when it comes to cationic branch stabilization.* We should point out here that there is a *range* of stabilities associated with α', α, and β sites, with slight overlap between ranges (Figure 2). This rule does not indicate *which* of two α sites, for example, would better stabilize a carbocationic branch, and so it only partially substitutes for an actual quantum chemical calculation.

Some Possibly Relevant Nonbay Ions

There are some molecules that may induce carcinogenesis by a route involving nonbay carbocation formation.[18] Examples are indicated in **16–22**. In each



case, the suggested route allows two choices for the ultimate position of the carbocationic branch. Our simple rule of the preceding section allows us to choose the energetically more favorable case. It is easy for us to predict that **19** should be more stable than **18**, since **19** places the branch on an α' site. For **21** and **22** we must recognize that the "branch" is now an allyl cation. The LUMO for this ion has a node at the middle carbon,[9] so the principal interaction of the branch with the PAH comes through the *tail* of the allyl fragment. In **21** the tail interacts with an α' site and in **22** with an α site, so **21** is predicted to be more stable (and calculations agree). This simple approach allows a qualitative sorting out of many ion stabilities reported in the literature.[14a–d]

Bay Region vs. K Region

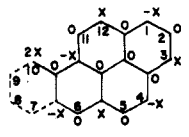
Since these two indices correlate with carcinogenicity, they correlate with each other,[6b,d,19] as Figure 3 shows. The solid points refer to K regions that are directly behind a bay region, like the unstarred K region in **7**. We call these *primitive* K regions. These points correlate very well with bay-region carbocation stability, and it has been shown that this is formally necessary.[19] The hollow points referring to nonprimitive K regions, like K* in **7**, correlate much less well with bay-region carbocation stability. When we reexamine[19] the data used by the Pullmans[4c] to arrive at their theory, we find that over 60% of those K regions are primitive. This enabled them to find a correlation with carcinogenicity that is, in essence, equivalent to that shown by bay-region carbocation energies but with a good deal of

(18) Eisenstadt, E.; Gold, A. *Proc. Natl. Acad. Sci.* **1978**, *75*, 1667.
(19) (a) Lowe, J. P. *Int. J. Quantum Chem., Quantum Biol. Symp.* **1982**, *9*, 5–13. (b) Lowe, J. P. *Int. J. Quantum Chem.* **1982**, *22*, 1221–1247.

scatter due to the presence of nonprimitive K-index values.

Influencing Carbocation Stability with Substituents

Once we have settled on a place for the cationic branch—say it is to be a bay-region ion—how can we guess whether some change in the PAH will stabilize or destabilize the ion, relative to its diol–epoxide precursor? Let us consider first the case of methylation. The main way that a methyl substituent can stabilize such a carbocation is by donation of methyl electronic charge to the π system of the ion—a process called *hyperconjugation*.[20] Hyperconjugation is larger when the methyl group is attached at the site with larger absolute magnitude of the lowest unfilled MO (LUMO) of the ion.[21] For example, the LUMO of the bay-region carbocation resulting from metabolism of benzo[*a*]pyrene (BP), **3**, is shown in **23** (along with the numbering scheme of BP). These LUMO coefficients all have one of two absolute values, either 0 or 0.302. We should expect hyperconjugative stabilization of the carbocation to be significant and of comparable magnitude when the methyl group is at positions 1, 3, 4, or 12. No significant hyperconjugative stabilization should result from methylation at positions 2, 5, 6, or 11. Quantum chemical calculations[12f] bear this out, although the degree of agreement depends upon the kind of calculation. Simple Hückel calculations generally give essentially perfect agreement with LUMO coefficient trends.[12d,e] More sophisticated methods, which are sensitive to steric interactions as well as hyperconjugation, show some deviations from the above expectations when the methyl group is close to the reacting terminal ring.[12f] Therefore, we are limited to using the hyperconjugation argument and the LUMO coefficients for "remote" methyl substitution,[12d] which means positions 1–5 and 12 in **23**.



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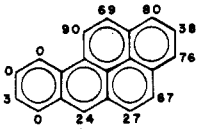


24

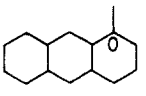
Observed[22] mouse-skin tumor-initiating activity[23] of monomethyl derivatives of BP (percent of mice with tumor) is shown in **24**. The remotely methylated systems fall into two ranges of activity with the least active cases (2- and 5-methylbenzo[*a*]pyrene) corresponding to methylation at points where the carbocation LUMO equals zero.[24]

Steric effects resulting from non-benzo-ring substitution at positions such as 11 in BP (called "bay-region substitution") and 6 in BP (called "peri substitution") are partially understood as a result of experimental[25a] and theoretical[6e,12f,25b–d] studies. Bay-region substitution promotes steric crowding in the bay region, and this crowding is more severe in the diol–epoxide than in the triol–carbocation, so the ion is computed[6e,12f] to be stabilized relative to its precursor. Steric crowding in the bay region due to non-benzo-ring substitution appears also to affect the relative stabilities of different conformations of bay-region diol–epoxides making more stable a form (of the syn diastereomer) that is more tumorigenically active.[25] Both of these effects are consistent with the observation[11] that bay-region substitution of a PAH generally produces a more active carcinogen. Methylation in the peri position of a PAH appears to influence the stereochemistry of the diol–epoxide and also its rate of formation in a manner that deactivates the molecule as a carcinogen.[11,26] (However, the datum in **24** for 6-methylbenzo[*a*]pyrene is an exception to this generalization.) The loss of tumorigenicity when BP is methylated in positions 7–10 is surmised to result from methyl blocking of enzymatic oxidation of the terminal ring.

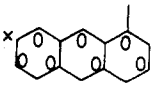
The practical conclusion, for our purposes, is that LUMO coefficients serve as a reasonably good guide for relative methylated carbocation stabilities and as a somewhat rougher guide for PAH tumorigenicities, with the added proviso that bay-region methylation activates and peri-methylation deactivates the PAH.

One might think that a computer calculation is needed in order to obtain LUMO coefficients like those in **23**, but this is not the case. A simple pencil-and-paper calculation suffices,[9b,27] as we shall now demonstrate using the carbocation resulting from the bay-region epoxide of benz[*a*]anthracene (BA), **2**.

To obtain LUMO coefficients for a carbocation that has been created by adding a branch to a fused benzene ring system: (1) sketch the π system and place a zero at the point where the branch joins the ring system (**25**); (2) place zeroes around the system at every second carbon (**26**); (3) at a spot far from the branch and on

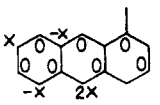


25



26

a nonzeroed carbon, place an x (**26**); (4) move from this x along the molecule, requiring that each zeroed carbon have adjoining coefficients that sum to zero (**27**, **28**); (5)



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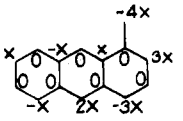


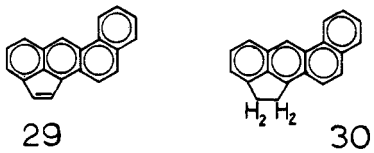
28

(20) Mulliken, R. S. *Tetrahedron* **1959**, *5*, 253–274.
(21) Fujimoto, H.; Fukui, K. In "Chemical Reactivity and Reaction Paths"; Klopman, G., Ed.; Wiley: New York, 1974; pp 23–54.
(22) Iyer, R. P.; Lyga, J. W.; Secrist, J. A., III; Daub, G. H.; Slaga, T. J. *Cancer Res.* **1980**, *40*, 1073–1076.
(23) Most of the evidence favoring the diol–epoxide mechanism of tumor initiation has been obtained from tumor initiation–promotion experiments on mouse skin.
(24) BP itself produced skin tumors on 67% of the mice.[22] This suggests that there is a general deactivating factor associated with methylation of BP (perhaps due to size or shape) and that hyperconjugative stabilization compensates for this when methylation occurs at remote positions 1, 3, 4, or 12. One is generally more confident about comparisons between isomers than between molecules that are more grossly different.
(25) (a) Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Jerina, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 4970–4972. (b) Silverman, B. D. *Cancer Biochem. Biophys.* **1982**, *6*, 23–29. (c) Silverman, B. D.; Laplaca, S. J. *J. Chem. Soc., Perkin Trans. 2* **1982**, 415–417. (d) Silverman, B. D. *Cancer Biochem. Biophys.* **1983**, *6*, 131–136.
(26) Yang, S. K.; Chou, M. W.; Fu, P. P. In "Carcinogenesis: Fundamental Mechanisms and Environmental Effects"; Pullman, B., Ts'o, P. O. P., Gelboin, H., Eds.: D. Reidel Publishing Co.: Dordrecht, 1980; pp 143–156.
(27) Longuet-Higgins, H. C. *J. Chem. Phys.* **1950**, *18*, 265.

for a normalized LUMO, require that the sum of squares of coefficients equal 1 (from **28**, $42x^2 = 1$, so $x = 1/(42)^{1/2} = (0.154)$.

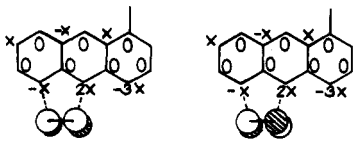
Even if we ignore the final step, we can still tell which positions should be methylated for minimal or maximal effect on ion stability.

The carbocation LUMO can be used to understand other types of substitutional effects as well.[14b] Consider molecules **29** and **30**, which can be viewed as resulting



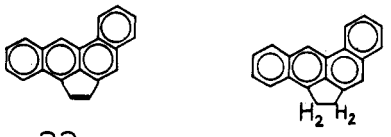
29 30

from substituting, respectively, an ethene or an ethane fragment for hydrogens at positions 7 and 8 of BA. We can understand the effect on bay-region carbocation stability in terms of the interaction between the carbocation LUMO and the HOMO of the ethene or ethane fragment, as depicted in **31** and **32**, respectively.



31 32

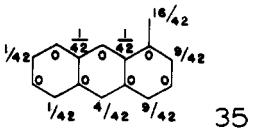
With ethene, the HOMO is C–C bonding; the ethene-carbon π AOs in this HOMO have the same phase and therefore must show phase *disagreement* across one of the links to the ion LUMO, prior to wave function readjustment. The opposite holds for ethane. Its HOMO is C–C π antibonding and has phase agreement with the LUMO of the ion. In addition, this antibonding HOMO lies at higher energy than does the donor MO in a methyl group, making the ethane fragment a more effective hyperconjugator. As a result, the diol epoxide of **29** is predicted to ionize in the bay region less easily than BA (**2**), while that of **30** should ionize more readily. We refer to the effect represented in **32** as "phase-matched hyperconjugation", and find that it is greater than the effect we would predict by summing the effects of methylation at positions 7 and 8 of BA. Since the BA carbocation LUMO is larger at position 6 than at 8, we expect that **33** should be even more deactivated



33 34

than **29** and that **34** should be more activated than **30**. Calculations[14b] of ion stabilities agree. (The possibility that **29** and **33** may proceed through nonbay ions like **18** and **19** suggests that additional potential activation pathways should be investigated.[28])

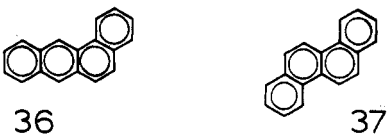
The carbocation LUMO can also be used to predict the effects of certain heteroatomic substitutions.[13b,c] Cations of the types we are considering have their positive charge spread over the whole molecule, and this distribution is given, at the simple Hückel level, by the squares of the LUMO coefficients. This means that the ion with LUMO **28** has the charge distribution given by **35**. One way to make formation of such an ion more



35

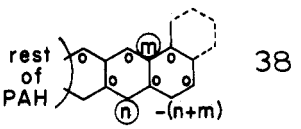
difficult is to replace a carbon with a (more electronegative) nitrogen at a site where significant positive charge would develop. It follows at once that the bay-region ion of **5** should be significantly harder to form than that of **4**. This agrees with the observation[15] and **5** is more deactivated than **4**. (The greater electronegativity of nitrogen affects all MO's, so even **4** is somewhat harder to ionize than the unsubstituted molecule **2**.) Presumably a nitrogen in the 6-position of BA (which develops a charge of 9/42) would deactivate BA even more than it does in the 7-position.[13c] An appropriate electropositive element (arsenic?) might reasonably be expected to have an activating effect.

There is one other kind of change whose effect on bay-region carbocation energy can be predicted by using LUMO coefficients—that induced by rearrangement of the rings in the conjugated system. For example, it is possible to argue from simple considerations[19] that the bay-region ion for **36** should be easier to form than that for **37** (though this will be at least partially offset by



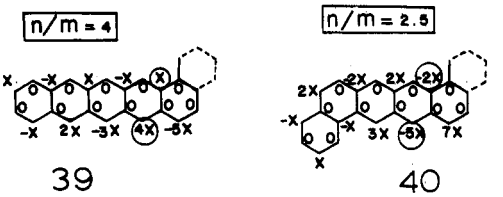
36 37

the fact that **36** has fewer bay regions than **37**). The ion stability is related to the ratio of two coefficients in the LUMO shown circled in **38**. The greater the



38

ratio n/m, the more stable is the carbocation.[19] It is easy to show that this ratio is equal to 2 for **36** and $^1/_2$ for **37**, so **36** should form a bay carbocation more easily. But one can produce an even simpler rule. We do this by observing (**39**) that a straight run of benzene rings



39 40

leads to a constant coefficient along the top of the structure, with all augmentation going on below, leading to a maximum n/m. If a "kink" occurs in the run (**40**), a crossover occurs in the coefficients. Once past the kink, the augmentation occurs only below, but some advantage has been lost relative to a straight run over an equal number of rings. The simple rule which results is that a kink reduces an ion's stability and is more destabilizing the closer it occurs to the bay region. This

(28) Sangaiah, R.; Gold, A.; Toney, G. E.; Toney, S. H.; Claxton, L.; Eastering, R.; Nesnow, S. *Mutat. Res.* **1983**, *119*, 259–266.

(29) Hecht, S. S.; Loy, M.; Hoffmann, D. In "Polynuclear Aromatic Hydrocarbons: Chemistry, Metabolism, and Carcinogenesis"; Freudenthal, R. I., Jones, P. W., Eds.; Raven Press: New York, 1976; Vol. 1, p 325.

rule can only be used to compare unbranched PAHs having the same number of rings but different arrangements of kinks or different numbers of rings with the same arrangements of kinks. In effect, it allows for a limited refinement in our $\alpha' > \alpha > \beta$ rule: **39** and **40** are both α cases, and we are now able to predict that **39** is the more stable.

Concluding Remarks

Simple rules allow one to prescreen certain kinds of PAH and related molecules for likelihood and/or degree of tumorigenic activity. The rules are based on an emerging picture of the chemical process by which certain PAHs lead to the induction of tumorogenesis and are supported by quantum chemical calculations as well. Because of our incomplete understanding of the reactions involved in this chemical process, predictions of relative tumorogenicity/carcinogenicity will sometimes be wrong, even when they are correct about the relative stabilities of ions. Despite this risk, the approach outlined here is useful since it requires little effort, often gives correct predictions, and, when it does not, provides a clue that the tumorogenic activity of the molecule in question is not controlled by the energy of formation of the triol–carbocation from the diol–epoxide.

An Introduction of Chiral Centers into Acyclic Systems Based on Stereoselective Ketone Reduction

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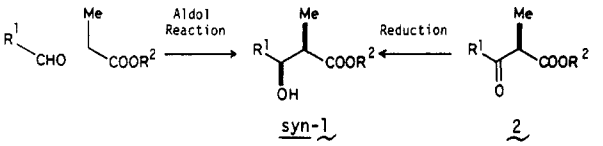
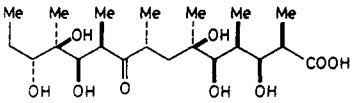
In connection with synthetic studies of polyoxomacrolide antibiotics, stereocontrolled reactions in acyclic systems have been extensively investigated. Among them, the stereoselective synthesis of *syn*-α-methyl-β-hydroxy esters **1** has attracted the attention of many synthetic organic chemists, since these moieties repeatedly appear in the framework of the above antibiotics (for example, erythronolide A seco acid, see Scheme I). Moreover, these moieties are an important building block for the synthesis of a complex array of methyl and hydroxyl functions involved in these natural products. Efforts have been focused mainly on the development of the regio- and stereocontrolled aldol reaction, and excellent results have been accumulated.[1] Alternatively, we undertook to synthesize the desired syn compounds **1** by a route based on their biogenesis, namely, by a stereoselective reduction of the corresponding α-methyl-β-keto esters **2**.

The polyoxomacrolide and polyether antibiotics are biogenetically classified as polyketides, and their carbon skeletons are believed to be constructed by a series of condensation of enzyme-bound acetate, propionate, or butyrate with the corresponding malonates. Quite recently, it was firmly established by two groups[2,3] that

Scheme I
Synthetic Routes for *syn*-α-Methyl-β-hydroxy Esters





Erythronolide A seco-acid

the oxygen atoms of the first-formed macrolide or polyether aglycons originated from precursor propionates. These findings strongly suggest that the absolute configurations of most of the hydroxyl groups should be set up by direct enzymatic reduction of the corresponding β-keto esters or poly-β-ketone intermediates.

Our primary approach began with an effort to design a chemical process corresponding to the enzymatic reduction of α-alkyl-β-keto esters in the hope of constructing multichiral centers involving hydroxyl groups.

Reduction of α-Methyl-β-Keto Esters (Type 1 Reduction) and α-Methyl-β-Hydroxy Ketones (Type 2 Reduction) with $Zn(BH_4)_2$

Our working Yamaguchi[9a] for the formation of *syn*-**1** was that if two oxygen functions in α-methyl-β-keto esters **2** are arranged to come to the same plane by coordination with a complex metal hydride reagent, hydride anion should attack the carbonyl carbon from

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Tadashi Nakata was born in Japan in 1943, received his B.S. and M.S. degrees from Hokkaido University, and then joined RIKEN, where he worked with the late Dr. Akira Tahara. He received his Ph.D from Hokkaido University in 1974 and spent 2 years at Harvard University with Prof. Yoshito Kishi as a postdoctoral fellow. Since then, he has been engaged in the synthesis of polyoxomacrolide and ionophore antibiotics.

(1) Masamune, S.; Choy. W. *Aldrichimica Acta* **1982**, *15*, 47. Evans, D. A. *Ibid.* **1982**, *15*, 23. Heatcock, C. H. In "Current Trends in Organic Synthesis"; Nozaki, H. Ed.; Pergamon Press: Oxford, U.K., 1983; p 27.
(2) Cane, D. E.; Taylor, P. B.; Liang, T-C. *Tetrahedron* **1983**, *39*, 3449.
(3) Hutchinson, C. R. *Acc. Chem. Res.* **1983**, *16*, 7.

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