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# MODEL CALCULATIONS FOR REACTIVITIES OF POLYCYCLIC AROMATIC HYDROCARBON METABOLITES

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Abstract: Structure-resonance theory calculations correlate reactivities and mutagenicities of polycylic aromatic hydrocarbon metabolites.

Aromatic hydrocarbons undergo enzymatic oxidation to yield (in part) arene oxides, phenols, and dihydrodiols.[1] Some of these metabolities are believed to lead to further oxidation products that are potent mutagens and carcinogens. In particular, the biological activities[2,3] of "bay-region" diol epoxides[4] have helped to implicate the diol epoxides as a class of principal ultimate carcinogenic aromatic hydrocarbon metabolites. The fact that epoxides bind covalently to cellular components[5], and observations of the chemical reactivities of diolepoxides support the bay-region hypothesis.[6] The results of several investigations also support the suggestion that formation of a stabilized carbocation by spontaneous or acid-catalyzed opening of the epoxide ring mediates both in vitro and in vivo chemistry.[7] Arene oxides undergo similar ring-opening reactions with subsequent formation of phenols or nucleophilic substitution products.[8]

Hückel and perturbational molecular orbital theory (HMO and PMO) have recently been extensively used to test carbocationic intermediates as models for chemical and biological activities of the aromatic hydrocarbon metabolites.[4,8,9] The purpose of this paper is to point out that structure-resonance theory (RT), generally found to be in better agreement with experiments and with SCF-MO calculations,[10] provides a more accurate standard for comparisons of structures and reactivities related to carcinogenicity.

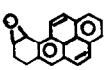
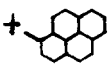
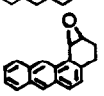
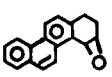
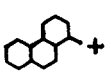
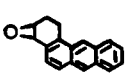
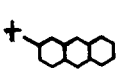
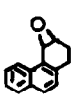
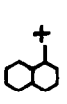
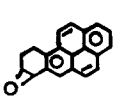
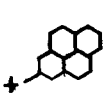
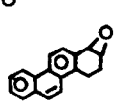
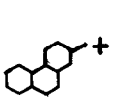
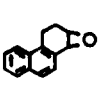
For discussions of the stabilities or ease of formation of cations, the comparisons of chemical reactivity with calculations given in Table I are pertinent.[11-13] The difference between the $\pi$ delocalization or resonance energy of cationic intermediate and neutral reactant hydrocarbon is correlated with $\sigma^+$ in each case. The RT results are obtained by using the algorithm, resonance energy = C logSC,[11,14] where C is a constant and SC (structure count) is the number of principal resonance structures. The RT(1) correlation assumes that C is identical for the neutral reactant and the cationic intermediate. Two optimum values of C are determined by regression analysis in the RT(2) calculation. The structures can be counted by making drawings, or by using pencil and paper graph-theoretical procedures.[15]

Successful qualitative attempts have been made to correlate the biological activities of bay-region epoxides with HMO or PMO estimates of the $\pi$-system energy differences, $\Delta E$, of epoxide and cation.[4] In a quantitative study, there was a linear relationship between $\Delta E$(PMO) and the

Table I. Cationic Reactivities of Polycyclic Aromatic Hydrocarbons.

| Reaction Type | Method of Calculation | Corr. Coeff. with $\sigma^+$ |
|---|---|---|
| Aromatic substitution (protodetritiation).[12] $\sigma^+$ for 26 positions in 15 compounds. Wheland-type cation intermediate. | HMO | 0.873 |
| | PMO | 0.900 |
| | RT(1) | 0.977 |
| | RT(2) | 0.980 |
| Solvolytic reactions (acetolysis of arylmethyl tosylates).[13] $\sigma^+$ for 14 compouds. Arylmethylium cation intermediate. | HMO | 0.915 |
| | PMO | 0.946 |
| | RT(1) | 0.937 |
| | RT(2) | 0.987 |

Table II. Mutagenic Activities[a] and Cation Stabilization Energies for Tetrahydroepoxides.

| Reactant(R) | Cation(C) π-system | Log Mutagenic Activity | C/R SC Ratio | Log SC Ratio | ΔE (HMO) | ΔE (PMO) |
|---|---|---|---|---|---|---|
|  |  | 4.64 | 27/6 | 0.653 | 0.868 | 0.794 |
|  |  | 4.35 | 16/4 | 0.602 | 0.848 | 0.766 |
|  |  | 4.37 | 23/6 | 0.584 | 0.826 | 0.713 |
|  |  | 3.93 | 18/5 | 0.556 | 0.803 | 0.639 |
|  |  | 3.72 | 14/4 | 0.544 | 0.770 | 0.628 |
|  |  | 3.27 | 10/3 | 0.523 | 0.812 | 0.658 |
|  |  | 3.24 | 19/6 | 0.501 | 0.717 | 0.488 |
|  |  | 3.11 | 16/5 | 0.505 | 0.736 | 0.526 |
|  |  | 2.36 | 9/3 | 0.477 | 0.744 | 0.545 |
| Correlation coefficient with log mutagenicity | | | | 0.951[b] | 0.778 | 0.848 |

[a]Revertants /nmol. These data made available by Dr. A. W. Wood. [b]RT(2), corr. coeff. 0.963.

logarithm of mutagenic activities ($His^+$ revertants /nmol/plate) for 9 tetrahydroepoxides with a correlation coefficient (r) of 0.74.[16] When the data for two phenanthrene derivatives were omitted, r was a respectable 0.96. The PMO results are compared in Table II with HMO and RT estimates of $\Delta E$. The recalculated PMO r is somewhat higher than reported previously, but the more significant result is that the highly correlative RT calculations support the chemical reactivity model, and they show that no basis for neglecting data is descernable.

The direction of ring-opening of arene oxides leading to phenols, the regioselectivity of nucleophilic attack, and the direction of dehydration of dihydrodiols or dihydrodiol esters have all been rationalized using PMO theory and assuming carbocation intermediates.[8] The qualitative results of RT are also in correspondence to the experimental selectivities. However, a comparison of the number of appropriate cation structures with the qualitative product studies will not be given at this time. The counting of structures is a trivial problem, and the reader may verify such results for himself.

Both qualitative and quantitative applications of molecular orbital or resonance theory, used as outlined above, are successful. Therefore the proposal[8] that reactivities of aryl and arene oxides are predictable is reasonable. Table II illustrates that the potential predictability is also high when theory is applied to a biological reaction with a well-defined chemical mechanistic basis. RT calculations seem to be somewhat more useful for this purpose. It should be noted that the rates of other types of reactions of aromatic hydrocarbons are likewise in excellent quantitative agreement with RT calculations.[11] The ease of calculations, and the possible extensions in a quantitative sense, should encourage the use of resonance theory in future chemical or biological rate and product studies.

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References and Notes

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