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REPRODUCTION OF MAJOR REACTIONS OF AROMATIC CARCINOGENS WITH GUANOSINE, USING HMO-BASED POLYELECTRONIC PERTURBATION THEORY

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Molecular orbital theory has now progressed to the point at which activation energies for unimolecular reactions of numerous small molecules can be calculated with satisfying accuracy, while mechanisms for simple bimolecular displacements (such as fluoride exchange on fluoromethane) can be compared by plotting reaction potentials for various possible pathways. These accomplishments suggest that the attack of reactive metabolites of non-reactive chemical carcinogens on nucleic acid bases can be similarly predicted. The reaction of benzo(a)-pyrene-7,8-diol-9,10-oxide with guanine, however, involves a system of 168 valence electrons. A basis set this large precludes determining a reasonable number of possible reaction potentials by ab initio methods, while the alternative of using a semi-empirical SCF-MO method, such as MINDO/3, would still require more money than would be spent simply to carry out the reaction and identify the products.[1] An alternative approach would be to ask whether some formal mixing of orbitals calculated separately for each of the reacting species gives an adequate representation of the more rigorously calculable reaction pathways. If this could be accomplished, then a preferred reaction for this particular pair of molecules could be calculated at a modest cost. It then becomes feasible that such calculations might be performed on many compounds, and that the results obtained be used as one of the variables incorporated into quantitative structure-activity methodologies intended to correlate carcinogenicity with chemical structure. We have tested this proposition with the simplest calculation method available, applied to cations believed to arise from some aromatic carcinogens. Our results are satisfyingly correlated with experimental data, and thus support the usefulness of the concept. They further suggest that higher quality calculation methods, applied similarly, will reliably predict the sites of reaction of many carcinogens

with nucleosides, as well as the overall extent of reaction.

Methods. The reactions of esters of N-hydroxy-N-arylacetamides are considered to involve N-aryl-N-acetylnitrenium ions as intermediates[2], while reactions of N-arylhydroxylamines are correspondingly considered to proceed via N-arylnitrenium ions. Hence, the reactions of such compounds with nucleosides are treated as the reactions of the corresponding nitrenium ions. The reactions of benzylic halides are treated as the reactions of the corresponding carbonium ions. The HMO calculations were carried out as described previously.[2]

The likelihood of a bond forming between atom r of a nucleophile and atom s of an electrophile may be said to depend on the energy of the perturbation which develops as these atoms approach each other, expressed as:[3]

$$\Delta E = \Sigma_m \Sigma_n \frac{2(C_r^m)^2(C_s^n)^2 \beta^2}{E_m - E_n} \qquad (1)$$

β is the resonance integral for the pair of atoms, while C_r^m and C_s^n are the coefficients at atoms r and s of the occupied orbitals of energy E_m and the unoccupied orbitals of energy E_n, respectively. The resonance integrals were based on Streitwieser's extended review of the rationales for selecting resonance integrals for heteroatom bonds in HMO calculations.[4] The values chosen were $\beta_{c-c} = 0.9$, $\beta_{c-n} = 0.8$, $\beta_{c-o} = 0.7$, $\beta_{n-o} = \beta_{n-n} = 0.6$. The degree of accessibility of electrophile to nucleoside base was also introduced into equation 1 as a modification of β dependent on the dihedral angle between the p_z orbitals on atoms r and s. Based on Corey-Pauling-Koltun molecular models (which included the ribose of the nucleosides), the dihedral angle γ was chosen to be 30, 45, 60 or 75 degrees. The value for β to be entered into equation 1 (now β') was obtained from the following set of equations:[4]

$$\beta' = \beta \frac{S'/(1 + S')}{S/(1 + S)} \qquad (2)$$

$$S' = S_{\pi\pi}\cos\gamma \qquad (3)$$

where $S_{\pi\pi}$ is taken to be 0.28.

Results. A table of solutions to equation 1 is given for five compounds with known reactions described in the literature. Among these are four aromatic amine derivatives and one polycyclic aromatic hydrocarbon derivative. We

note that three different reactions with guanosine are found among these five compounds, and that they are all correctly identified by this simple calculation method. Esters of N-hydroxy-2-acetamidofluorene, N-hydroxy-4-acetamidobiphenyl and N-hydroxy-2-acetamidophenanthrene all react with guanosine in the same manner, to attach the nitrogen of the amide to C-8 of guanine.[5-7] N-Hydroxy-1-naphthlamine, on the other hand, attacks O^6 of guanine preferentially in DNA, but also via its N atom.[8] 7-Bromomethylbenz(a)-anthracene attacks a position different from either of these, the 2-amino group.[9]

Thus, the simplest method available for predicting preferred reactions between unique pairs of reagents successfully identified the major adduct in reactions yielding three different types of products. Understandably, we have found cases in which the prediction is in error, in certain of these instances presumably because the HMO method is unable to deal with non-bonding electrons such as the lone pair on N-3 of cytosine. However, we would be greatly surprised if this method were not more generally applicable when based on a high quality all-valence-electron calculation method.

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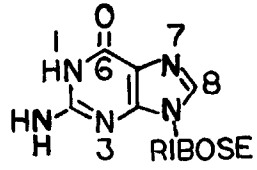
Reactions of electrophiles with guanosine[a]



GUANOSINE

Position of attack on guanosine	N-acetyl-N-2-fluorenyl-nitrenium ion		N-acetyl-N-4-xenyl-nitrenium ion		N-acetyl-N-2-phenanthryl-nitrenium ion		N-1-naphthyl-nitrenium ion		(7-benzanthracenyl)-carbonium ion
	(3)	(N)	(3)	(N)	(1)	(N)	(4)	(N)	($R-CH_2^+$)
1	0.14	0.02	0.14	0.02	0.10	0.02	0.18	0.06	0.19
3	0.03	0.03	0.03	0.02	0.05	0.03	0.08	0.02	0.09
7	0.14	0.07	0.14	0.06	0.21	0.07	0.16	0.10	0.23
8	0.10	<u>0.26</u>	0.20	<u>0.30</u>	0.17	<u>0.34</u>	0.11	0.22	0.28
N^2	0.19	0.08	0.18	0.08	0.27	0.09	0.22	0.20	<u>0.37</u>
O^6	0.17	0.04	0.18	0.04	0.15	0.05	0.19	<u>0.28</u>	0.31

[a]Sign conventions were chosen so that a higher ΔE value indicates a more favorable reaction. The known predominant reactions of precursor compounds are indicated by underlining.