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REACTIVITY CRITERIA AND THE PURINE MOLECULE

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Recently some statements were made in this journal[1] in response to a preliminary communication[2] submitted concerning a series of SCMO calculations[3]. In this note[2] we called attention to some correlations between our computed pi-electron densities and certain chemical and physical properties of purine. Certain errors were made in the text of the comment on our note which we feel should be corrected.

It was asserted[1] that in two previous calculations on purine, one a Hückel calculation[4] and the other an SCF determination[5], the results with respect to the relative order of electron densities agreed with each other. We have collected those results in Table I together with some other results which seem pertinent. It seems clear from the table (cols. 3,4) that those former two calculations in fact do not agree. Furthermore, the comment concerning the inappropriateness of our comparison with Mason's[6] Hückel results is also not well founded if columns 1,2 and 3 are compared.

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[1] B. Pullman, Tetrahedron Letters, No. 4, 231 (1963).

[2] R.L. Miller and P.G. Lykos, Tetrahedron Letters, No. 11, 493 (1962).

[3] R.L. Miller, P.G. Lykos, and H.N. Schmeising, J. Am. Chem. Soc. **84**, 4623 (1962).

[4] A. and B. Pullman, Bull. Soc. Chim. France 766 (1958).

[5] A. Veillard and B. Pullman, J. Theoret. Biol. **4**, 37 (1963).

[6] S.F. Mason, Ciba Foundation Symposium on The Chemistry and Biology of Purines, p. 72 (1957).

In reference 2 in the commentary on our note there are compared three ways of handling the fact that the pyrrole-type nitrogen is different from the pyridine-type nitrogen in the purine molecule and within the context of Hückel theory. Columns 2 and 3 of Table I display some of these results where it is clear that there is in fact no difference in the order of the relative charge densities. Moreover the order found does agree with Mason's Hückel results (Col. 1). In our calculation in which the two possible tautomers of purine were considered, different orders of relative charge densities were found (Cols. 5,6). Furthermore the pyrrole-type nitrogen was so designated on the basis of a comparative calculation in which the pi-energy and the sigma compression energy of each of the tautomers were determined. The assignment was then made to correspond to that form having lowest total energy[3]. Hence the statement[1] about an <u>ab initio</u> assignment of nitrogen species seems inappropriate.

TABLE I

Some SCMO and HMO Pi-electron densities for Purine

Atom[a]	1[b]	2[c]	3[d]	4[e]	5[f]	6[g]
N1	1.266	1.195	1.193	1.218	1.270	1.330
N3	1.283	1.216	1.202	1.250	1.240	1.347
C2	0.844	0.902	0.907	0.819	0.794	0.741
C6	0.864	0.907	0.918	0.828	0.781	0.758
C8	0.820	0.895	0.879	0.889	0.910	0.816

a. For the numbering refer to reference 3.

b. A Hückel result[6] in which the two imidazole nitrogens are equally weighted, but more heavily than the nitrogens in the pyrimidine ring.

c. A Hückel result[4] in which N9 is designated the pyrrole nitrogen.

d. A Hückel result[4] in which N7 is desigated the pyrrole nitrogen.

e. An SCF result[5] in which N7 is designated the pyrrole nitrogen

f. An SCF result[2,3] in which the pyrrole-nitrogen has been designated as N7 to correspond to the lower molecular energy.

g. An SCF in which the pyrrole-nitrogen has been designated as N9 and corresponds to the higher energetic form.

The further remark was made that electron density should be expected to be relevant in discussions of nuclear magnetic resonance spectra. This may be so, but in the discussion given in the commentary some important details were left out. Even if the conjecture of the Jardetskys'[7] were to be accepted as an experimental fact (that C6 is the most shielded carbon atom), the two calculations cited in the critique[4,5] (Cols. 3,4) differ from each other in precisely this regard, and thus cannot both be in agreement with that speculation. To give a balanced picture it should be further noted that the Jaretzkys' based their hypothesis on the assumption that the negative charge is distributed equally between the pyrimidine and imidazole nitrogens. This assumption is neither bourne out by our calculation[2,3] nor by the other results referred to[4,5]. It is interesting to note, in this connection, that one of the co-authors of the previous SCF work[5] has recently published a paper concerning the interpretation of NMR spectra[8]. One of the spectra to which he turns his attention is that of purine due to the Jardetzkys'. He concludes that C8 has the

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[7] C.D. Jardetsky and O. Jardetsky, J. Am. Chem. Soc. **82**, 222 (1960).

[8] A. Veillard, J. chim. phys. **59**, 1056 (1962).

highest charge density which is in agreement with our results[2,3] and in disagreement with the statements made in the criticism of our note[1].

We were criticized for having used relative pi-electron charge densities in the isolated molecule (in its ground state) as an index for relative reactivity to electrophilic attack. It should be apparent from the proliferation of reactivity criteria such as pi-density[9], free valency[10], frontier electron density[11], localization energy[12], self-consistent localization energy[13], super delocalizability[14], etc., that the matter is far from settled. Indeed, the complications of solvation effects and perhaps the explicit identity of other reactants may have to be introduced before a satisfying measure of success will be realized. In fact, the theoretical framework of the pi-electron approximation, as it is ordinarily employed, includes uncertainties of sufficient magnitude that it would really be difficult to say a priori that any one of the several reactivity criteria is, or is not, valid. Even if the adequacy of the pi-electron approximation were to be accepted[15], the role of geometry and the structure and internal consistency of the basic parameters which enter the theory are still not well understood[16]. Accordingly it

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[9] E. Huckel, Z. Physik **72**, 312 (1931).

[10] C.A. Coulson and P. and R. Daudel, Rev. Sci. **85**, 29 (1947).

[11] K. Fukui, T. Yonezawa, and H. Shingu, J. Chem. Phys. **20**, 722 (1952).

[12] G.W. Wheland, J. Am. Chem. Soc. **64**, 900 (1942).

[13] H.N. Schmeising and R.L. Miller, to be published. Presented by R.L.M. at 140th National Meeting of ACS, Sept., 1961.

[14] K. Fukui, T. Yonezawa, and C. Nagata, Bull. Chem. Soc. Japan, **27**, 423 (1954).

[15] P.G. Lykos, J. Phys. Chem. **66**, 2324 (1962).

[16] P.G. Lykos, J. Chem. Phys. **35**, 1249 (1961).

seemed worth noting a result in which the simplest reactivity criterion was adequate in characterizing a fairly complex and unsymmetric pi-electron system.

Finally we are unable to appreciate why there is being attempted a distinction[1] between Fukui's idea[11] in which the highest occupied and lowest unoccupied molecular orbitals are explicitly considered (and generally referred to as Frontier Electron Theory), and the designations PHOO (plus haute orbitale occupée), PBOL (plus basse orbital libre)[5]. We may also remark in this regard that these MO's and the corresponding Lagrangian multipliers are unique because of the constraint in the closed-shell matrix representation of Hartree-Fock theory that the epsilon matrix be diagonal[17]. The expectation value of any observable will be invariant to a unitary transformation of the occupied MO's among themselves and the unoccupied MO's among themselves for that wave function. However, such a transformation could modify both the so-called PHOO and PBOL in a large variety of ways. Koopmans' theorem[18] shows that the diagonality constraint on the epsilon matrix may have some significance in assessing ionization potentials. Other ways of taking up that degree of freedom may also be useful[19].

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[17] C.C.J. Roothaan, Rev. Mod. Phys. **23**, 69 (1951).

[18] T. Koopmans, Physica **1**, 104 (1953).

[19] See T.L. Gilbert in Molecular Orbitals in Chemistry, Physics, and Biology, Ed. by B. Pullman and P.O. Lowdin, Academic Press, Inc. New York, to be published (1963). Also K. Ruedenberg and C. Edmiston, Rev. Mod. Phys., July, 1963.