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# CHARGE DENSITIES, CHEMICAL REACTIVITY AND BASICITY OF PURINE.

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In a recent note Miller and Lykos[1] opposed self-consistent molecular orbital calculations on purine to older Hückel-type calculations on the same molecule. They seem to have made on that occasion a certain number of mistatements.

The Hückel-type molecular orbital calculations on the distribution of electronic charges in purine (and biochemical purines)[2,3,4] do not correlate quite satisfactorily with the chemical reactivity of this molecule or its basicity. This is in no way surprising since these calculations refer to the <u>isolated</u>, unreacting molecules. We have shown[4] that the introduction of polarisation effects (localization energies) leads on the contrary to a very satisfactory agreement between predicted and experimental chemical reactivity (for a great number of biological purines and pyrimidines[5]). A fundamental treatment due to Nakajima and A. Pullman[6] has also demonstrated that the basicity of polyazaheterocyclics <u>cannot be considered as depending solely in the $\pi$ charges of the nitrogens</u> but is determined by a more complex function. Applied to a wide series of purines and pyrimidines this treatment yielded an excellent agreement bet-

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[1] R.L. Miller and P.G. Lykos, <u>Tetrahedron Letters</u>, N°11, 493 (1962).

[2] A. Pullman and B. Pullman, <u>Bull. Soc. Chim. France</u> 766 (1958).

[3] T. Nakajima and B. Pullman, <u>Bull. Soc. Chim. France</u> 1502 (1958).

[4] B. Pullman, <u>J. Chem. Soc.</u> 1621 (1959).

[5] A. Pullman and B. Pullman, <u>Quantum Biochemistry</u>, Wiley's Interscience Division, New-York, in press.

[6] T. Nakajima and A. Pullman, <u>J. de Chimie Phys.</u> 793 (1958).

ween calculated and observed basicities and was able to predict the position of the most basic nitrogen in a large series of these molecules. These predictions have been entirely confirmed by experiment[7].

Miller and Lykos have calculated the charge densities in purine by a semi-empirical self-consistent field molecular orbital procedure. These calculations refer, too, to the isolated molecule. In this particular case they correlate better directly with the reactivity and the basicity of purine than do the Hückel calculations but it is a naive viewpoint to imagine that, for this reason, they are more significant in this respect than the Hückel ones. Neither chemical reactivity nor the basicity depend directly on the charge distribution in the isolated molecule, so that a Hückel treatment including polarisation effects may be fundamentally more reliable in this respect than an approximate SCF treatment neglecting such effects. Numerous results show[5] that the localization energies agree very satisfactorily with observed chemical reactivities and there are stricking examples in which SCF charges do not[8]. We must add also that we have carried out recently ourselves SCF calculations not only on purine but on a large series of purines and pyrimidines[9]. In the particular case of purine our results are in disagreement with those of Miller and Lykos : in our SCF results the relative order of the charge densities on the C and N atoms of purine is the same as the one obtained by the Hückel method.

Other techniques than reactivity or basicity must be looked for in order to settle discussions on charge distribution in isolated molecules. Proton magnetic resonance may be such a technique. The chemical shifts of the protons give information about the electronic densities of the C atoms carrying these protons : the most shielded proton must belong to the carbon with the greatest charge density. Under this assumption

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[7] See e.g. G.P. Wheeler, Cancer Res., 22, 651 (1962) ; P. Brookes and P.D.Lawley, J. Chem. Soc. 539 (1960) ; 3923 (1961) ; B.C. Pal Biochemistry, 1, 558 (1962) ; H.G. Windmueller and N.O. Kaplan, J. Biol. Chem. 236, 2716 (1961).

[8] See e.g. S. Kolboe and A. Pullman, Colloque International sur le Calcul des Fonctions d'Onde Moléculaires. C.N.R.S. 1958, p.213.

[9] A. Veillard and B. Pullman, J. Theret. Biol. in the press.

Jardetsky's measurements[10] indicate e.g. that $C_6$ of purine has the highest electronic density among the hydrogen-carrying carbons of the molecule. This is in agreement with our Hückel and SCF calculations and in disagreement with those of Miller and Lykos.

Two more remarks : a) Miller and Lykos seem to ignore our own calculations on the basicities of purines which, moreover, are based on a SCF treatment ; b) these authors seem to attach a great importance to the fact that they distinguish between the two nitrogens of the imidazole ring of purine by considering $N_9$ (which they number $N_7$) as contributing two $\pi$ electrons to the system. In this respect we must stress that not only did we always proceed in this way but that we have even compared, on the very particular example of purine, the results of different possible treatments following different assumptions about the N atoms of the imidazole ring of purine[2]. A similar comparison for a large number of purines was made by Fernandez-Alonso[11]. Moreover this situation makes the comparison indicated in Table I of Miller and Lykos illogical because they compare their calculations which distinguish ab initio between $N_7$ and $N_9$ of purine with those of Mason[12] who does not make any such distinction between these atoms. Finally we must add that, contrary to the statement by Miller and Lykos, we have never considered the role of frontier electrons in the chemistry of purine.

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[10] C.D. Jardetzky and O. Jardetzky, J. Amer. Chem. Soc. 82, 222 (1960).

[11] J.I. Fernandez-Alonso and R. Domingo, Anal. Fis. y Quim. (Madrid), 56 B, 687 (1960) ; J.I. Fernandez-Alonso in J. Garcia Blanco (Ed.), Quimica Fisiologica, Vol.II, p.657, Saber, Valencia, 1961.

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