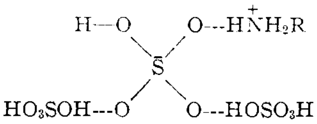
methane Pocker[8] has presented good evidence for the stability of the $ClHCl^-$ ion.

Because the hydrofluoride ion FHF^- is so familiar even to an aquocentric chemistry, $ClHCl^-$ does not seem as difficult to accept as the combination of bisulfate ion with additional acid molecules which our results require. The principle is not in fact new, we suppose that the hydrogen atom of the acid bonds with unshared electrons on the oxygen atoms in the bisulfate ion in the same way that the hydrogen atoms in HF bond with unshared electrons in the fluoride ion. It is true that the oxygen atoms in the bisulfate ion can have only very weakly basic properties, but it is also true that the hydrogen atoms in sulfuric acid are extremely acidic, and hydrogen bonding depends as much on the acidity of the hydrogen donor as it does on basicity of the acceptor.

It seems necessary then to conclude that the remarkably non-water-like quality of the chemistry of acid–base reactions in nitromethane should be attributed to the lack of hydrogen bonding donor properties of this solvent, and that conversely the familiar properties of acid–base systems in water-like solvents must be attributed much more to the quality of these solvents as hydrogen bonding donors and much less to their relatively high dielectric constants than has usually been the case.[16]

Our picture of the indicator salt in solutions of sulfuric acid of concentration over 0.1 *M* would in fact be



and we expect the stability of similar structures to be an important factor in the chemistry of all solvents which lack the hydrogen bonding donor properties of water and of other solvents which, like water, contain relatively acidic hydrogen atoms. Because of the close parallelism which often exists[17] between the equilibrium of the salt, formation of indicators and the rates of acid-catalyzed reactions, we expect also that the rates of acid-catalyzed reactions in non-water-like solvents will frequently depend upon a higher power than the first of the acid concentration and that such reactions will often be retarded by the addition of "neutral" salts even though a catalysis by the lyonium ion is out of the question.[18]

---

[16] See however ref. 13.

[17] Recently reviewed by F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 935 (1957).

[18] Such a retardation is observed in the effect of tetramethylammonium *p*-nitrobenzoate on the mutarotation catalyzed by *p*-nitrobenzoic acid of tetramethylglucose in nitromethane; E. L. Blackall and A. M. Eastham, THIS JOURNAL, **77**, 2184 (1955).

NEW YORK, N. Y.

[CONTRIBUTION FROM THE LABORATORY OF THEORETICAL CHEMISTRY, THE UNIVERSITY OF PARIS]

On the Hydrogenation of Purines[1]

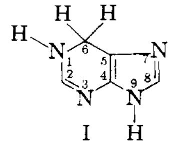
BY T. NAKAJIMA AND B. PULLMAN

RECEIVED FEBRUARY 10, 1959

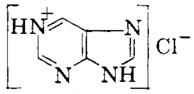
The reduction of purine hydrochloride under one atmosphere of hydrogen in the presence of palladium–charcoal catalyst at room temperature, and the inertness under the same conditions of purine and the biological purines: adenine, guanine and xanthine, are interpreted in terms of the relatively great value of the free valence—and correlatively small value of the radical localization energy—of carbon 6 of purine hydrochloride.

We have studied in a series of recent publications the electronic structure of purines in relation to their chemical and physicochemical properties[2–4] and with the principal object of establishing a correlation between the structure and the antitumor activity of purine antimetabolites.[5] This note is concerned with the interpretation of some recent observations on the hydrogenation of purines.

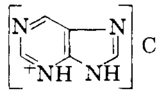
Bendich[6] has shown that *purine hydrochloride* may be reduced under one atmosphere of hydrogen in the presence of 5% palladium–charcoal catalyst at room temperature. The product obtained has been considered tentatively to be 1,6-dihydropurine (I). *Purine itself* does not reduce under these conditions and neither do the "biological" purines: adenine, guanine and xanthine.



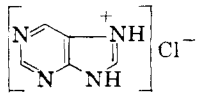
There are three possible structures for purine hydrochloride with the proton attached, respectively, to N_1, N_3 or N_7. Following our theoretical investigation on the position of the most basic nitrogen on the skeleton of purine, it is the structure II which is the most probable.[3,4]



II



III



IV

---

[1] Supported by Public Health Service Grant C-3073.

[2] A. Pullman and B. Pullman, *Bull. soc. chim. France*, **25**, 766 (1958).

[3] A. Pullman, *ibid.*, **25**, 641 (1958).

[4] T. Nakajima and B. Pullman, *ibid.*, **25**, 502 (1958).

[5] B. Pullman and A. Pullman, *ibid.*, **25**, 973 (1958), and in press.

[6] A. Bendich in "The Chemistry and Biology of Purines," A. Ciba Foundation Symposium, Churchill Ltd., London, 1957, p. 308.

Compd.	Carbon	π-Electronic charge	Free valence	Localization energy (in β units)		
				Radical	Nucleophilic	Electrophilic
	2	0.902	0.402	2.445	2.323	2.567
Purine	6	.907	.456	2.329	2.176	2.482
	8	.895	.443	2.285	2.176	2.393
	2	.827	.444	2.281	2.052	2.512
Purine	6	.805	.494	2.142	1.847	2.437
cation II	8	.891	.443	2.284	2.158	2.410

The upper part of the table contains the results of calculations, by the molecular orbital method,[7] of the distribution of electronic charges and free valences on the carbons of *purine* as well as their localization energies for a radical, a nucleophilic or an electrophilic substitution.[8] The last type of index represents the approximate relative activation energies for the corresponding substitutions on these carbons.[8] The lower part of the table contains the same results for the *purine cation* (II). The transition from the neutral molecule to the cation is being accounted for by the change of the coulomb integral of the nitrogen atom which, with the usual notations,[7] is put equal to $\alpha_N = \alpha_C + 0.4\beta_{CC}$ and $\alpha_{NH} = \alpha_C + \beta$.

The most plausible essential step in the reduction under the specified conditions is the attack on the carbon atoms of the purine skeleton by atomic hydrogen. The atom most susceptible to such an attack should thus be the carbon characterized by the greatest free valence or the smallest radical localization energy.[7,9] As far as free valence is concerned, the greatest value of this index in both purine and its cation is that of carbon 6, which should thus be the starting center for the reduction. Moreover, the value of the free valence of carbon 6 is much greater in the purine cation than in purine itself, which may account for the reduction of purine hydrochloride and the inertness of purine itself. The result is confirmed by the examination of the radical localization energies: this energy is appreciably smaller for carbon 6 of the purine cation than for carbon 6 of purine itself. As a matter of fact it should nevertheless be noticed that while the smallest radical localization energy in purine cation is associated with carbon 6, it is associated with carbon 8 in purine itself. The disagreement with the indications of free valence makes it uncertain to predict which carbon should be attacked preferentially by free radicals, in purine. Nevertheless the radical localization energy for carbon 8 of purine is appreciably higher than that of carbon 6 of the purine cation so that in any way the reduction of the cation and the inertness of the neutral purine are accounted for.

The impossibility of reducing, under the same conditions, the "biological" purines: adenine, guanine and xanthine may be satisfactorily accounted for in the same scheme. Following our previous theoretical study of the basicity of these molecules,[4] we shall assume that in their hydrochlorides the proton is attached to N_1 in adenine[10] and to N_7 in guanine and in xanthine. The difficulty in reducing these compounds may be attributed in the first place to the very small value of the free valence of carbon 6 in all of them (it is equal, *e.g.*, to 0.139 in adenine), owing to the presence of a substituent on this atom. Moreover it may be calculated easily that the free valences of the remaining carbons in these biological bases and in their cations should be appreciably smaller than the free valence of carbon 6 in the purine cation. Thus the closeness of the values of the free valences of carbons 2 and 8 of adenine to those of the same carbons in purine suggests similar values for the free valences of these positions in the corresponding cations, and as to the free valence of carbon 8 (the only unsubstituted one) in guanine and xanthine and in the corresponding cations, it is calculated to equal 0.463 and 0.464, respectively, in the two bases and approximately 0.475 in their cations.

Thus, it is the particularly high value of the free valence of carbon 6 of the purine cation or, in equivalent terms, the particularly low value of its radical localization energy which seems to account satisfactorily for the apparently exceptional possibility of reducing the purine hydrochloride within the conditions utilized by Bendich.

13 RUE PIERRE CURIE
PARIS, FRANCE

---

[7] For the description of the method, see, *e.g.*, B. Pullman and A. Pullman, "Les Théories Électroniques de la Chimie Organique," Masson et Cie., Ed., Paris, 1952, pp. 173–213.

[8] G. W. Wheland, THIS JOURNAL, **64**, 900 (1942).

[9] For a recent general discussion on free valence in organic molecules and localization energies, see B. Pullman and A. Pullman, "Progress in Organic Chemistry," Butterworth Publ., London, 1958, pp. 31–71.

[10] This result seems to be confirmed by the X-ray study of the crystals of adenine hydrochloride, W. Cochran, *Acta Cryst.*, **4**, 81 (1951).